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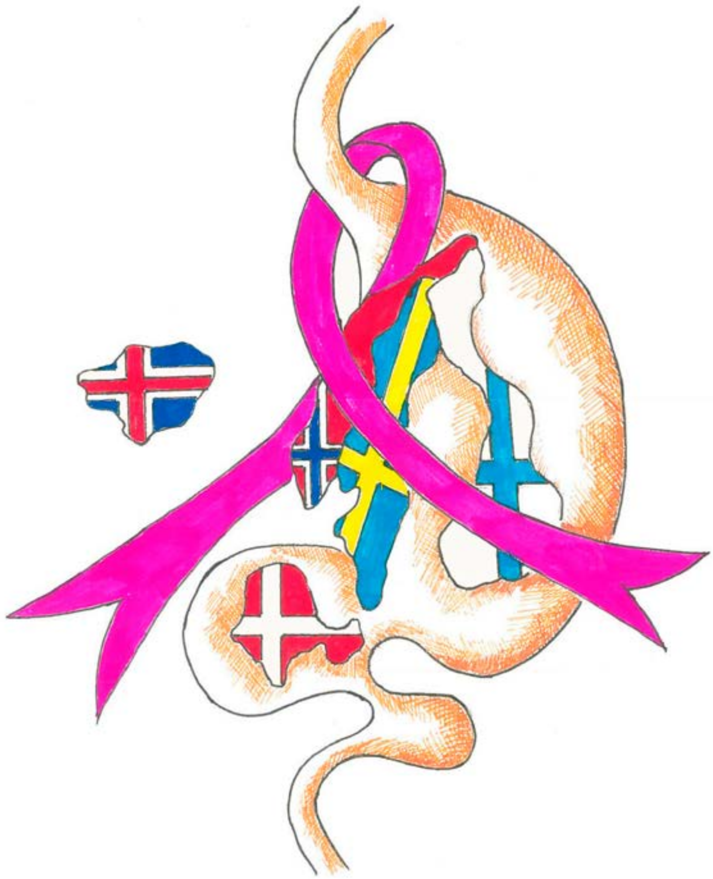
Cancer after bariatric surgery: risk and prognosis



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CANCER AFTER BARIATRIC SURGERY: RISK AND PROGNOSIS

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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In memory of my grandparents

ABSTRACT

Obesity is a major public health challenge with a rapidly growing prevalence worldwide. The condition increases the risk of multiple diseases, including cancer in different locations. Current evidence on the effect of intentional weight loss on cancer is inconclusive. Bariatric surgery results in extensive and sustained weight loss with positive impact on several obesity-related comorbidities. It can therefore serve as a proxy for intentional weight. The few studies available suggest that bariatric surgery may decrease overall cancer risk but increase the risk of cancer in specific tumor locations. This thesis assesses the impact of bariatric surgery on cancer risk and cancer mortality using the Nordic Obesity Surgery Cohort (NordOSCo). The cohort includes individuals with an obesity diagnosis recorded in the National Patient Registries in any of the five Nordic countries between 1980 and 2012. **Study I and IV** included Swedish cohort members only, while **Study II and III** included the entire cohort.

Study I validated bariatric surgery codes in the Swedish Patient Registry and the Scandinavian Obesity Surgery Registry (SOReg) against medical records for bariatric surgery performed during 2011. The accuracy of the codes proved to be high; 93.5% in the Patient Registry and 98.6% in SOReg. However, one fifth of the procedures in SOReg were not registered in the Patient Registry, indicating that the completeness of bariatric surgery registrations in the Patient Registry can be improved.

Study II evaluated the association between bariatric surgery and the risk of obesity-related cancer, non-obesity related cancer and cancer in selected sites. The study found an overall decreased risk of cancer following bariatric surgery that was more evident for cancers associated with obesity, particularly breast cancer, endometrial cancer and non-Hodgkin lymphoma in women. The lower cancer risk was primarily observed during the initial years following surgery and this decrease diminished with time after surgery. In contrast, the risk of kidney cancer was increased among bariatric surgery patients.

Study III and IV focused on colorectal cancer and studied the impact of bariatric surgery on the risk and prognosis of this disease. Incidence rates of colon cancer were higher in bariatric surgery patients than in the general population, especially after ≥10 years post-surgery. The elevated incidence rates exceeded that of obese individuals without bariatric surgery. No associations were observed for rectal cancer. On the contrary, cancer-specific mortality after rectal cancer diagnosis was more than three-fold increased among bariatric surgery patients compared to obese individuals without this surgery, but no differences in survival were observed between the exposure groups following colon cancer diagnosis.

In conclusion, the Swedish Patient Registry is a valid data source for research on bariatric surgery. Overall cancer incidence seems to decrease after bariatric surgery, but the effect varies between cancer sites with a possible increase in the risk of colon and kidney cancer. Bariatric surgery may also decrease the chance of survival in rectal cancer.

LIST OF SCIENTIFIC PAPERS

I. Wenjing Tao, Dag Holmberg, Erik Näslund, Ingmar Näslund, Fredrik Mattsson, Jesper Lagergren, Rickard Ljung.
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II. Wenjing Tao, Giola Santoni, My von Euler-Chelpin, Rickard Ljung, Elsebeth Lynge, Eero Pukkala, Eivind Ness-Jensen, Pål Romundstad, Laufey Tryggvadottir, Jesper Lagergren.
Cancer Risk after Bariatric Surgery in a Population-Based Cohort Study from Five Nordic Countries.
Manuscript submitted

III. Wenjing Tao, Miia Artama, My von Euler-Chelpin, Mark Hull, Rickard Ljung, Elsebeth Lynge, Guðríður Helga Ólafsdóttir, Eero Pukkala, Pål Romundstad, Mats Talbäck, Laufey Tryggvadottir, Jesper Lagergren.
Colon and Rectal Cancer Risk after Bariatric Surgery in a Multi-Country Nordic Cohort Study.
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Effects of Obesity Surgery on Overall and Disease-Specific Mortality in a 5-Country Population-Based Study.
Gastroenterology. 2019;157(1):119-127

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
DALY	Disability-Adjusted Life Year
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICD	International Statistical Classification of Diseases and Related Health Problems
ICD-O	International Classification of Diseases for Oncology
IGF-1	Insulin-like Growth Factor 1
NOMESCO	Nordic Medico-Statistical Committee
NordOSCo	Nordic Obesity Surgery Cohort
NQR	National Quality Registry
PPV	Positive Predictive Value
QoL	Quality of Life
RCT	Randomized Clinical Trial
RR	Relative Risk
SHBG	Sex Hormone Binding Globulin
SOReg	Scandinavian Obesity Surgery Registry
SIR	Standardized Incidence Ratio
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

CONTENTS

1 INTRODUCTION

Obesity and cancer are two major global public health challenges that are growing in scale with increasing economic prosperity and aging demographics.[1,2] The health care needs associated with these conditions are putting substantial pressure on health systems that are already stretched to their limits. One of the important questions to address is therefore – how can society meet the future health care needs of its aging population with an increasing prevalence of obesity and cancer?

A key public health intervention is prevention. There are clear links between obesity and multiple diseases requiring substantial health care resources, including type 2 diabetes mellitus (T2DM), cardiovascular diseases and cancer.[3] In fact, obesity is associated with cancer in no less than thirteen sites, and the list keeps growing.[4] Bariatric surgery has emerged as the only long-term effective treatment for morbid obesity, resulting in sustained weight-loss, improvement of comorbidities and prolonged life expectancy. However, this surgery may also lead to unintended outcomes such as increased risk of alcohol and drug dependency,[5,6] and possibly colorectal cancer.[7,8] Far from all eligible patients are given the opportunity to undergo bariatric surgery, and opponents to publicly financed bariatric surgery argue that the health benefits do not necessarily offset the costs associated with surgery. Evaluation of the long-term benefits and consequences of this procedure would therefore provide policy makers with useful information when prioritizing health care resources.

Since bariatric surgery did not become widespread until relatively recently, there are few epidemiological studies with follow-up exceeding ten years. This limitation impedes on the interpretation of findings related to outcomes that take time to develop, such as cancer. Indeed, the paucity of research on intentional weight loss and cancer has been highlighted by the International Agency for Research on Cancer (IARC).[4]

This thesis, consisting of four original studies, builds on a cohort of obese individuals from five Nordic countries with up to three decades of follow-up. The aim is to assess the long-term impact of bariatric surgery on cancer incidence and cancer prognosis that can inform clinicians and policy makers.

2 BACKGROUND

The Global Burden of Disease consortium estimated that the global prevalence of obesity in 2015 was 12% in adults and 5% in children, which is equivalent to 604 million adults and 108 million children with obesity.[1] Obesity is associated with several comorbidities, including cardiovascular diseases, cancer, T2DM, chronic kidney failure, musculoskeletal disorders, gastroesophageal reflux disease, liver steatosis, gallbladder disease, and sleep apnea.[9] Taken together, it is estimated that 4 million deaths and 120 million disability-adjusted life years (DALYs) were attributed to excess body weight in 2015; cancer contributed to almost 10% of these excess deaths and DALYs.[1]

2.1 Defintion of obesity

There are several measurements of body weight or body composition, including waist-to-hip ratio, waist-to height ratio, waist circumference, percent body fat, and body surface area. Body mass index (BMI) is the most widely used measurement and is calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). The World Health Organization (WHO) defines overweight as BMI $\geq$ 25 kg/m^2 and obesity as BMI $\geq$ 30 kg/m^2 in adults. Obesity is subdivided into three classes and the highest class (morbid obesity) is equivalent to BMI $\geq$ 40 kg/m^2.[10]

However, there are a few caveats associated with BMI. The measurement does not provide details on body fat distribution or composition, and is often underestimated in elderly and overestimated in muscular individuals. In fact, abdominal obesity might be more strongly associated with cardiovascular disease, T2DM, and cancer than BMI.[11] Furthermore, the BMI threshold for overweight and obesity may not be appropriate for all ethnicities, as studies have observed that the association between BMI and percent body fat differs between ethnic groups.[12] However, owing to its simplicity and accessibility, BMI will likely remain one of the most widely used and studied measurements for body weight or composition.

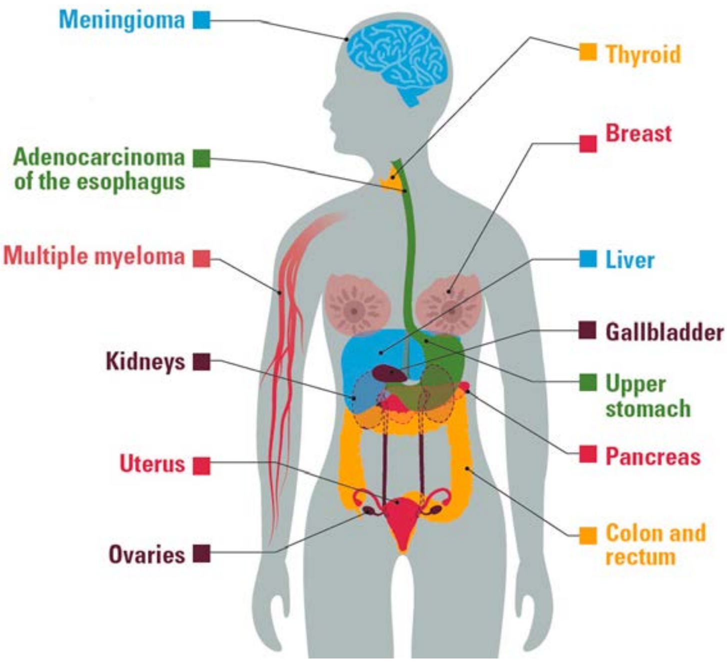
2.2 Obesity and cancer

2.2.1 Obesity and cancer risk

According to IARC, obesity is associated with cancer in thirteen sites: esophagus (adenocarcinoma), gastric cardia, colon, rectum, liver, gallbladder, pancreas, breast (postmenopausal), corpus uteri, ovary, kidney (renal-cell), meningioma, thyroid, and multiple myeloma (Figure 1). The increase in relative risk (RR) is highest for endometrial cancer (RR 7.1; 95% CI 6.3-8.1) and esophageal adenocarcinoma (RR 4.8; 95% CI 3.0-7.7). Limited evidence of an association was observed for fatal prostate cancer, diffuse large B-cell lymphoma and male breast cancer.[4] An umbrella review of systematic reviews and meta-analyses confirmed the association for the above mentioned sites, with the exception of thyroid cancer and meningioma.[13]

Positive dose-response relationships between obesity and cancer incidence in several studies support causality. A meta-analysis found that every 5 kg/m^2 increase in BMI was strongly associated with the increased risk of several cancers, notably colon and thyroid cancer in men, endometrial and gallbladder cancer in women, and esophageal adenocarcinoma and kidney cancer in both sexes.[14] Weight-gain during adulthood increases the risk of postmenopausal breast, endometrial, and ovarian cancer in women, colon cancer in men, and kidney cancer in both sexes.[15] Longer duration of obesity, as well as obesity in childhood, adolescence, and early adulthood, has also been linked to higher risk of obesity-related cancers.[4,16]

In addition to evidence from epidemiological studies, experimental studies in animal models have found that obesity promotes tumorigenesis and cancer in the mammary gland, colon, liver, pancreas, prostate, skin, and leukemia.[4]



Modified illustration from Centers for Disease Control and Prevention, Atlanta, GA, USA

Figure 1. Thirteen cancer sites associated with obesity.

2.2.2 Obesity and cancer prognosis

Obesity is associated with increased cancer mortality, specifically in cancer of the esophagus, pancreas, colon, rectum, kidney, gallbladder, liver, multiple myeloma, and non-Hodgkin lymphoma in both sexes; prostate and gastric cancer in men; and breast, endometrium, cervix, and ovary cancer in women.[17-19] Some of this excess mortality results from higher cancer incidence, but several studies have also shown an association between disease-specific survival after cancer diagnoses and BMI around the time of diagnosis, notably for breast cancer, while some evidence is also available for endometrial, ovarian, colorectal, and prostate cancer as well as hematologic malignancies.[20-27] Studies on pancreatic cancer have shown conflicting results;[28,29] no association was observed for esophageal cancer;[30] and higher BMI was paradoxically associated with increased survival in kidney cancer.[31] Weight gain after cancer diagnosis has also been associated with higher cancer-specific and all-cause mortality.[32] Nevertheless, compared to studies on cancer risk the literature is sparse and less consistent.[4]

Multiple factors may contribute to the inverse association between BMI and cancer survival. Epidemiological studies suggest that obesity might be associated with larger tumor size and more aggressive tumor characteristics. For example, overweight and obese patients with breast and prostate cancer have an increased risk of tumor recurrence.[33,34] Delayed diagnosis might be another contributing factor as obese patients often present with more advanced tumor stage at diagnosis.[34,35] Furthermore, cancer patients with obesity face challenges related to clinical management and treatment of their cancer, such as insufficient dosing of chemotherapy, reduced efficacy of radiotherapy, and inferior outcomes after hormonal therapy.[36]

2.2.3 Mechanisms of action between obesity and cancer

Several pathways involving the endocrine, metabolic, inflammatory, and immune systems have been proposed to mediate the association between excess BMI and cancer (Figure 2).

Insulin resistance and increased insulin secretion is common in individuals with obesity. Chronic elevated levels of insulin result in heightened activity of the insulin-like growth factor 1 (IGF-1), which stimulates cell proliferation and migration, inhibits apoptosis, and enhances angiogenesis that are all linked to carcinogenesis. Elevated serum levels of IGF-1 have been observed for several malignancies.[37]

Insulin and IGF-1 also inhibit the synthesis of sex hormone-binding globulin (SHBG), the major carrier protein for testosterone and estradiol in plasma, and leads to elevated levels of bioactive sex steroids. Adipose tissue is also the main producer of estrogen in men and postmenopausal women, and contributes to elevated estrogen levels in obese individuals. Sex steroids regulate cell differentiation, proliferation and apoptosis.[38] In a pooled analysis of nine studies, women with higher concentration of sex steroids and decreased levels of SHBG had an increased risk of post-menopausal breast cancer.[39] Similarly, elevated levels of estrogen and androgen have been associated with an increased risk of endometrial cancer.[40]

Adipose tissue also synthesizes polypeptide hormones, such as leptin and adiponectin. Leptin is known for suppressing appetite, but also promotes cell proliferation, inhibits apoptosis, and stimulates angiogenesis.[37] Some studies have found an association between leptin levels and the risk of prostate, colorectal, and breast cancer.[41-43] Adiponectin has anti-inflammatory properties and the opposite effect to leptin on cell growth, but its secretion is suppressed by insulin and estrogen. Epidemiological studies have found an inverse association between plasma concentrations of adiponectin and cancer of the endometrium,[44] breast,[45] prostate,[46] and possibly colon and rectum.[47]

Additionally, obesity is associated with low-grade chronic inflammation, abnormal release of cytokines and acute-phase reactants, and activation of pro-inflammatory signalling pathways that might stimulate carcinogenesis.[38] Finally, studies have proposed that mechanical and oxidative stress might also contribute to the obesity-cancer relationship.[48]

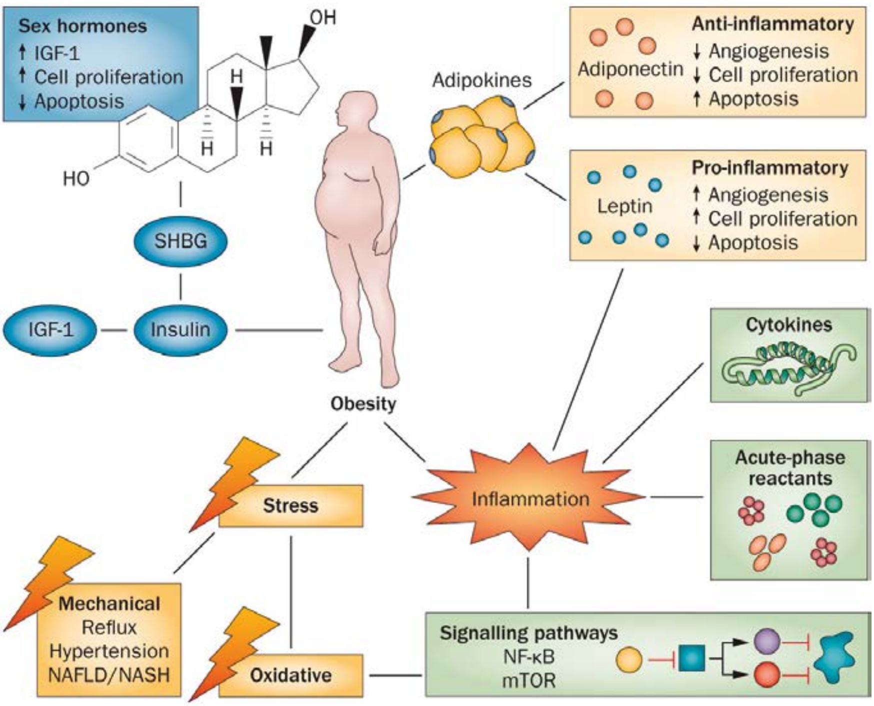


Illustration from Tao W et al. Nat Rev Clin Onc, 2013;10:519-33

Figure 2. Proposed mechanisms of action linking obesity to cancer.[36]

2.2.4 Weight loss and cancer

Although plenty of literature supports an association between obesity and cancer, the impact of weight loss on cancer etiology and cancer outcomes is ambiguous.

Preclinical studies have observed that calorie restriction inhibits tumor growth.[49] There are also some epidemiological evidence supporting an association between intentional weight loss and decreased cancer risk. One study reported that intentional weight loss of ≥ 20 pounds in women reduced the risk of any cancer, and cancer in the breast, colon, and endometrium.[50] Overweight and obese women who lost enough weight to reach the normal range of BMI had a cancer risk equivalent to normal-weight women.[50] Intentional weight loss of ≥ 5% might also be associated with a decreased risk of breast and endometrial cancer,[51-53] but this potential association could not be confirmed by all studies.[54] A randomized clinical trial (RCT) of women free of cancer at baseline concluded that dietary interventions could decrease the risk of breast cancer and increase breast cancer survival.[55] In contrast, no such benefit was observed for colorectal cancer or obesity-related cancer overall, but weight loss from the intervention in this study was modest and averaged 2.2 kg during the first year.[56,57]

In general, published literature on this topic is sparse and inconclusive. Some studies rely on self-reported weight loss that is vulnerable to biases. Another challenge is the difficulty of distinguishing between intentional and unintentional weight loss. The latter is associated with increased morbidity and mortality, and might mask any association between weight loss and cancer outcomes. Additionally, it is difficult to separate the effect of weight loss from that of physical activity, diet, and other lifestyle changes. Finally, although weight loss can be achieved through diet restriction, behavioral modifications, physical activity, and medical therapy, few of these conventional treatments have resulted in clinically meaningful weight loss in the long term, especially among individuals with morbid obesity.[58] Bariatric surgery typically leads to substantial and long-lasting weight reduction and has served as a proxy for intentional weight loss in research.

2.3 Bariatric surgery

2.3.1 Weight loss and health benefits of bariatric surgery

Health benefits derived from bariatric surgery have been demonstrated in several observational studies and a few RCTs. Bariatric surgery patients typically report a weight reduction of 25–30% within the first three years of surgery, compared to 4–7% with medical therapy or lifestyle interventions.[59-62] Sustained weight loss has been reported up to ten years after surgery.[3]

The impact of bariatric surgery on morbidity, quality of life (QoL), and mortality is relatively well-documented, especially for T2DM. A meta-analysis of sixteen studies reported that 64% of patients with T2DM experienced remission after surgery, compared to 16% in patients on medical therapy.[63] More recent RCTs have reported a T2DM remission rate of 30–70% up to five years after surgery.[59-62,64] Bariatric surgery can also improve hypertension, dyslipidemia, metabolic syndrome, obstructive sleep apnea, and musculoskeletal disorders, and have a protective effect on cardiovascular events, end-stage renal disease, and possibly cancer.[3,65-67]

According to a meta-analysis, bariatric surgery significantly improves QoL, although the impact varied considerably across studies.[68] In the RCTs that assessed QoL as one of the outcomes, a few or all of the eight QoL domains of the SF36 survey were improved up to five years after bariatric surgery.[61,64]

Finally, bariatric surgery seems to have an overall long-term survival benefit, although studies with more than ten years of follow-up are limited. Compared to conventional treatment or no treatment, bariatric surgery reduced overall mortality with 41% according to a meta-analysis of eight observational studies.[69] The risk reduction was greatest for T2DM (62–92%), followed by coronary heart disease (43–56%) and cancer (16–60%).[70,71] However, overall mortality rates in bariatric surgery patients remained nearly twice as high as in the corresponding general population, and the survival benefit of the surgery seemed to decrease with time.[71]

2.3.2 Bariatric surgery and cancer

2.3.2.1 Bariatric surgery and cancer risk

Cohort studies and meta-analyses have indicated that bariatric surgery might decrease overall cancer risk by 30–50%, with greater impact on obesity-related cancers than non-obesity related cancers.[72-79] Assessments of specific cancer sites have generated mixed results, with strongest evidence observed for endometrial and breast cancer. Pooled results from observational studies on endometrial cancer and breast cancer estimated risk reductions of 60% and 44%, respectively, after bariatric surgery.[80,81] In contrast, analyses of selected tumor sites in two meta-analyses found either no statistically significant associations between bariatric surgery and any of the individual tumor sites[78] or an association with breast cancer only.[79]

More recently, two matched cohort studies reported decreased risk of breast, endometrial, pancreatic, and prostate cancers.[7,72] However, the two studies seem to present contradictory results for colorectal cancer. One study observed a 40% decreased risk of colon cancer and no statistically significant association with the risk of rectal cancer,[72] while the other study found a more than two-fold increased risk of colorectal cancer.[7] The association in the latter study was only significant for gastric bypass, and no analyses were undertaken for colon and rectum separately.[7] Other studies on colorectal cancer seem to indicate an increased risk after bariatric surgery as well, but results from the few available studies are highly inconsistent.[8]

2.3.2.2 Bariatric surgery and cancer mortality

Cancer mortality rates seem to decrease after bariatric surgery, but there is limited research on this topic. One cohort study found a 46% reduction in cancer mortality after bariatric surgery, with no difference between obesity-related and non-obesity related cancers.[76] The authors of this study proposed that the lower cancer mortality rates in bariatric surgery patients were due to decreased cancer incidence, rather than increased cancer survival.[76] A Nordic study confirmed the findings from the previous study, but observed a significant difference only during the initial five years after bariatric surgery.[71] In fact, cancer mortality rates among bariatric surgery patients in this study were lower than the rates in the corresponding general population, indicating a potential selection bias where only individuals found to be free from cancer were probably considered for bariatric surgery.[71] To our knowledge, there are no studies evaluating cancer survival after cancer diagnosis in bariatric surgery patients.

2.3.2.3 Mechanisms of action between bariatric surgery and cancer

Based on the findings of a single study, bariatric surgery does not seem to have any independent effect on reduction of cancer risk, but the potential association is mediated through weight loss.[82] Multiple mechanisms by which bariatric surgery may reduce cancer risk have been proposed. For example, post-operative remission of T2DM might counteract the insulin- and IGF-1 mediated carcinogenic effects of obesity.[83] The level of SHBG might be restored as a result of improved insulin sensitivity that lowers circulating levels of bioactive sex steroids.[84] Bariatric surgery might also reduce plasma concentrations of estradiol and leptin, increase levels of adiponectin, decrease oxidative stress, and reduce chronic inflammation.[85]

2.3.3 Prevalence and indication of bariatric surgery

Due to its health benefits and the relative safety of the procedure, bariatric surgery has increased rapidly in popularity worldwide. In the United States, the number of procedures increased from 158,000 to 216,000 between 2011 and 2016.[86] According to a survey undertaken by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), 579,517 bariatric procedures were performed in 56 countries in 2014.[87] Although reporting was incomplete, the survey results provide an indication of the scale and the geographical distribution of countries where these procedures are performed.

The most common indication for bariatric surgery is BMI ≥ 40 kg/m^2 in the absence of obesity-related comorbidity, or BMI ≥ 35 kg/m^2 in the presence of at least one comorbidity. In reality, patients undergoing bariatric surgery often have BMI far above these thresholds.[88] Some guidelines specify an upper age limit of 60 years as the risk of postoperative morbidity and mortality increases with age.[89] However, more recent studies suggest that bariatric surgery is a safe procedure in patients aged ≥ 65 and they should not be excluded solely due to age.[90] Bariatric surgery in patients < 18 years is more controversial and evidence on long-term outcomes in this patient group is just beginning to emerge. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends that bariatric surgery can be considered in "carefully selected" pediatric patients with BMI > 40 kg/m^2 and severe comorbidities, or BMI > 50 kg/m^2 and mild comorbidities.[91]

There are no absolute contraindications to bariatric surgery, but relative contraindications include severe heart failure, unstable coronary artery disease, end-stage lung disease, active cancer treatment, portal hypertension, drug/alcohol dependency, and severe mental illness unresponsive to treatment.[92]

2.3.4 Mechanisms of action of bariatric surgery

Bariatric surgery procedures can be roughly divided into three categories based on their mechanisms of action: malabsorptive procedures that interfere with digestion and absorption; restrictive procedures that limit intake; and mixed malabsorptive and restrictive procedures that act through both mechanisms.[93]

Bariatric surgery leads to weight loss through multiple mechanisms, including 1) macronutrient and micronutrient malabsorption; 2) reduction in food intake and changes in food preferences; 3) altered secretion of gut hormones; 4) changes in gut microbiome; and 5) increased production of bile acids leading to improved metabolism. The type of bariatric procedure affects which mechanisms come into play.

In fact, it has been suggested that malabsorption induced by changes to the gastrointestinal anatomy accounts for <10% of reduction in total caloric intake after bariatric surgery.[94] More importantly, bariatric surgery patients seem to adopt dietary modifications with preference given to vegetables and fruits over high-caloric beverages and foods.[95] Changes in taste perception and food aversion, as well as early satiety and reduced hunger, also contribute to reduced daily caloric intake.[94]

Furthermore, bariatric surgery might alter the secretion of gut hormones with increased regulation of appetite and elevated insulin levels as a result. Dietary and anatomical modification can also result in major changes in the gut microbiome that might have beneficial effect on insulin sensitivity and adiposity. Finally, bariatric surgery increases plasma levels of bile acids that are associated with improved glucose and lipid metabolism.[94]

2.3.5 Bariatric surgery procedures

Historically, six main procedures of bariatric surgery can be identified and grouped according to their mechanisms of action:[96]

- **Malabsorptive**: Jejunoileal bypass;
- **Mixed malabsorptive and restrictive**: Roux-en-Y gastric bypass (gastric bypass) and biliopancreatic diversion with duodenal switch;
- **Restrictive**: Vertical banded gastroplasty, adjustable gastric banding (gastric banding), and sleeve gastrectomy.

According to the IFSO Global Registry, the most prevalent bariatric procedures between 2014 and 2018 was gastric bypass (53.2%) followed by sleeve gastrectomy (45.9%) and gastric banding (5.0%).[97] Figure 3 illustrates the most common procedures included in the studies of this thesis.

2.3.5.1 Jejunoileal bypass

Jejunoileal bypass was one of the first bariatric procedures and developed in the 1950s. This procedure circumvents most of the small bowel and leads to substantial and long-lasting weight loss. However, patients who underwent jejunoileal bypass were often afflicted with extensive complications such as electrolyte imbalance, vitamin and mineral deficiencies, severe diarrhea, gas bloat syndrome, kidney stones, and progressive liver degeneration. Consequently, most of these patients had their procedure reversed over time, and the procedure was eventually abandoned in favor of other safer procedures.[96]

2.3.5.2 Gastric bypass

The first gastric bypass was performed in 1967 and quickly rose in popularity as it proved to be as effective as jejunoileal bypass in achieving weight loss, but had fewer long-term complications.[93] Further modification of the procedure took place in the following years, and it is now the most widely performed bariatric procedure globally.[97] In this procedure most of the stomach, duodenum, and proximal jejunum are bypassed, and a jejunojejunostomy restores continuity with the biliopancreatic limb (Figure 3).

2.3.5.3 Biliopancreatic diversion with duodenal switch

The *biliopancreatic diversion* was first performed in the late 1970s and developed to avoid some of the complications associated with jejunoileal bypass. The procedure consists of a partial horizontal gastrectomy draining into a food limb through a gastrojejunostomy that joins the biliopancreatic limb to form the common segment. The *biliopancreatic diversion with duodenal switch* replaces the horizontal hemi-gastrectomy with a pylorus-saving vertical sleeve gastrectomy combined with a duodenoileostomy and a longer common segment (Figure 3). This procedure is reported to have fewer sides effects than biliopancreatic diversion.[93]

The biliopancreatic diversion with or without duodenal switch are technically difficult and time-consuming operations, but can offer better outcomes than the other bariatric procedures in terms of weight loss and remission of comorbidities.[98]

2.3.5.4 Vertical banded gastroplasty

The vertical banded gastroplasty was developed as an alternative to procedures with an enteric or gastric bypass, and widely performed in the 1980s and 1990s. In this procedure, a vertical stomach pouch is stapled and the outlet is restricted with a mesh or silicon band (Figure 3). However, complications such as stenosis of the outlet, rupture of staple line, and weight regain due to gastric pouch enlargement often required surgical revision. Eventually, this procedure was abandoned in favor of the laparoscopic gastric banding.[96]

2.3.5.5 Adjustable gastric banding

The adjustable gastric banding quickly became the procedure of choice in the 1990s and early 2000s. The procedure involves the placement of an adjustable band horizontally around the upper stomach to create a small pouch (Figure 3). The band was made adjustable by means of a silastic cuff that could be filled or drained with fluid from a subcutaneous valve. However, failure to achieve long-term weight loss and complications, such as band slippage and perforation, has led to a rapid decline in popularity.

2.3.5.6 Sleeve gastrectomy

Due to the high complication and mortality rates associated with biliopancreatic diversion with duodenal switch, the sleeve gastrectomy was proposed as a first-stage operation in a two-stage procedure. The sleeve gastrectomy consists of a longitudinal gastrectomy that leaves a tunnel-shaped gastric remnant with an intact pylorus. In many patients, weight-loss after this first-stage operation was sufficient and the second stage operation was no longer necessary.[93] Sleeve gastrectomy became a stand-alone procedure in the mid-2000s and is now the fastest growing bariatric procedure globally. However, long-term outcomes and complications are yet to be evaluated.[96]

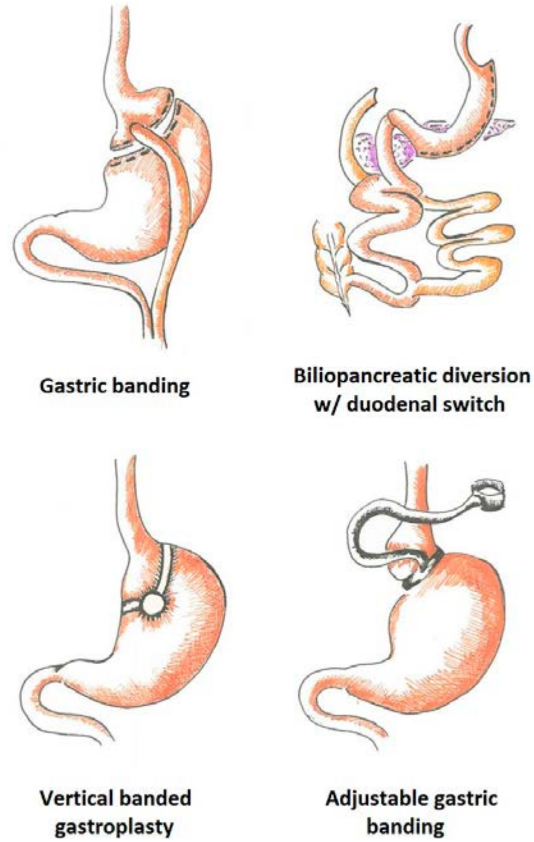


Illustration by Ketevan Kandelaki

Figure 3. Four bariatric surgical procedures: gastric banding, biliopancreatic diversion with duodenal switch, vertical banded gastroplasty, and adjustable gastric banding.

2.3.5.7 Complications and short-term mortality

Complication and perioperative mortality rates after bariatric surgery have decreased substantially since its first introduction, and are now comparable with several commonly performed surgical procedures such as cholecystectomy and coronary bypass surgery.[99] According to a meta-analysis, perioperative mortality was higher for mixed surgical procedures than for restrictive, and for open surgery than laparoscopic surgery.[69]

Complication rates vary substantially between studies and surgical procedures. The most serious early complication after bariatric surgery is anastomotic leak that has a mortality rate of 15%. Other early complications include anastomotic stenosis; bleeding at the staple line; and thromboembolic events.[100] Late complications from gastric banding include band slippage that may lead to obstruction and ischemia of the stomach wall in serious cases; band erosion; and dilation of the esophagus. Late complications after gastric bypass include marginal ulcers resulting in bleeding or perforation; internal hernia with small bowel volvulus; and gallstone disease.[100]

Side effects from bariatric surgery include dumping syndrome that appears after ingestion of high-calorie foods and leads to abdominal pain, nausea, tachycardia and light headedness; and micronutrient deficiency, primarily of iron, calcium, vitamin B_{12}, and vitamin B_9.

Reported risk factors for severe complications, including mortality, are older age, male sex, smoking, T2DM, congestive heart failure, hypertension, previous abdominal surgery, and hypoalbuminemia. [101,102]

3 AIMS

The overall aim of the thesis was to contribute to the body of knowledge on long-term outcomes after bariatric surgery, specifically focusing on cancer risk and prognosis.

To achieve this objective, a cohort was compiled as a central piece of this thesis consisting of individuals with obesity diagnoses in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). As bariatric surgery identified from the national patient registries was the exposure of interest, one of the objectives was to validate the bariatric surgery codes in these registries to ensure correct assignment of exposure status.

The four study-specific aims addressed in this thesis are:

- To assess the accuracy and completeness of bariatric surgery registrations in national health registries (**Study I**);
- To clarify the association between bariatric surgery and the risk of obesity-related and non-obesity related cancer (**Study II**);
- To specifically address the association between bariatric surgery and colorectal cancer risk (**Study III**);
- To assess the association between bariatric surgery and colorectal cancer prognosis (**Study IV**).

Since the hypothesis differs between colorectal cancer and other cancers in relation to bariatric surgery, these outcomes were addressed in two separate studies (**studies II and III**). In **study II**, we hypothesized that weight-loss through bariatric surgery reduces overall cancer incidence rates, particularly of obesity-related cancers. Based on previous findings, **study III** hypothesized that bariatric surgery increases the risk of colorectal cancer due to anatomical and physiological changes in the gastrointestinal tract induced by surgery.

4 MATERIALS AND METHODS

4.1 Overview

Table 1. Overview of the study design and statistical analyses in study I-IV.

	STUDY I	STUDY II	STUDY III	STUDY IV
Study design	Validation study	Cohort study		
Setting	Sweden	Denmark, Finland, Iceland, Norway, Sweden		Sweden
Study period	January 1 – December 31, 2011	January 1, 1980 – December 31, 2015		January 1, 1980 – December 31, 2012
Data sources	• Swedish Patient Registry • Scandinavian Obesity Surgery Registry • Medical records	• Patient Registries • Cancer Registries • Cause of Death Registries • Total Population Registries		
Inclusion criteria	Registrations of bariatric surgery in the two registries within the study period	Obesity diagnosis in the Patient Registries		Obesity diagnoses in the Patient Registry and colorectal cancer diagnoses in the Cancer Registry
Exposure	Not applicable	Bariatric surgery		
Main outcome(s)	Not applicable	Any obesity-related and non-obesity related cancer	Colon and rectal cancer	Colorectal cancer-specific mortality and all-cause mortality
Confounders	Not applicable	Sex, calendar period, length of follow-up, country, diabetes (only study II)		Sex, age at colorectal cancer diagnosis, education level, calendar period
Main statistical analyses	Positive predictive value (PPV)	• Cox proportional hazards model • Standardized incidence ratio (SIR)		Cox proportional hazards model

4.2 Data sources

This thesis builds primarily on data derived from nationwide registries in the Nordic countries. For **study I**, data from a quality registry and medical records were also obtained.

4.2.1 National health and population registries

The Nordic countries are widely known for their long history of nationwide population-based registries that were originally established for administrative purposes, but have since become important data sources for social and health-related research. There are a number of national registries containing a wealth of individual-level information about a country's residents. The most well-known for health-related research include the patient registry, cancer registry, cause of death registry, prescribed drug registry, medical birth registry, and the registry of the total population. Linkages between the registries are made possible by means of a unique individual identifier (personal identity code) assigned to all residents, making these data sources a "gold mine" for epidemiological research.[103] The studies in this thesis use data from the sources described below.

4.2.1.1 Patient registries

The national patient registries record all episodes of hospital care in the country and include information on patient characteristics and health care providers; dates of admission, operation and discharge; and codes for surgical procedures and discharge diagnoses.

Although the Nordic patient registries were established over a time period of three decades, the evolution of these registries has largely been the same and usually starts with somatic inpatient care to then gradually expand to psychiatric care, outpatient specialized care, and day surgery. Sweden was first to establish the patient registry in 1964, but nationwide coverage was not achieved until 1987. The patient registries in the other Nordic countries had complete national coverage nearly from inception (Table 2).

Discharge diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems (ICD) in all countries, but there may be country-specific modifications to the ICD codes. Introduction of new ICD versions occurred largely simultaneously across countries, with the exception of Denmark that migrated directly from ICD version 8 (ICD-8) to version 10 (ICD-10).[104]

Surgical procedures are coded based on the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures from the mid-1990s and onwards, and includes specific codes for bariatric surgery.[105] Country-specific coding systems of surgical procedures were used prior to NOMESCO, but did not include specific codes for bariatric surgery with the exception of Sweden.

The patient registries from primarily Denmark, Finland and Sweden have been validated through several studies, showing overall high accuracy but with substantial variation between diagnoses. Reviews of validation studies found positive predictive values (PPVs) ranging from 15%-100% in the Danish registry, 75%-

99% in the Finnish registry, and 85%-95% in the Swedish registry depending on diagnosis; trauma or injury and cardiac events turned out to be the most accurately recorded diagnoses.[106-108]

4.2.1.2 Cancer registries

The national cancer registries in all Nordic countries are nationwide, with a long history of mandatory reporting of cancer cases dating back to the 1950s and 60s.[109] Denmark is the sole exception, where reporting became mandatory only in 1987 (Table 2).[109] The cancer registries include information on date of diagnosis, topography, morphology, behavior or malignancy, patient demographics, and source of confirmation. Some registries also include tumor stage and treatment.[110] There is a high degree of completeness and comparability between the Nordic cancer registries, but some differences in registration practices exists, as detailed below.

Information on new cancers are collected from multiple sources, including hospitals and long-term care, primary care physicians, pathology and cytology laboratories, and death certificates. There are some differences in data sources between cancer registries in the Nordic countries, most notably for Sweden that is the only country where information from death certificates are not included.[110] It is estimated that this missing data source accounts for approximately 4% of all cancer cases[111] and the underreporting affects primarily cancers frequently diagnosed in advanced stages, such as pancreas, biliary tract, lung, esophagus, and liver cancer.[110] A Swedish validation study of pancreatic and biliary tract cancers found substantial underreporting of these cancers to the cancer registry when compared to the patient registry and cause of death registry. The study suggested that this discrepancy was due to the common use of imaging as the basis for diagnosis, rather than histopathological confirmation, at these tumor sites.[112]

There are also some differences in coding practices between countries that may affect cross-country comparisons of cancer incidence rates and interpretation of trends over time. These include differing rules for inclusion of premalignant and borderline malignant tumors that primarily affect tumors of the urinary bladder, brain, and central nervous systems; and different counting practices of multiple tumors in the same organ, which is especially relevant for paired organs (for example lung, breast, and kidney). Furthermore, variations in screening programs may affect comparability of cervical, breast, and colorectal cancer incidence between countries.[110]

4.2.1.3 NORDCAN

To provide comparable cancer data across the Nordic countries and address concerns related to differing coding practices over time, the NORDCAN database was initiated in 2002 by the Association of Nordic Cancer Registers and the

IARC. NORDCAN consists of information from the national cancer registries and converts the data into a uniform international standard by first recoding the tumors into the International Classification of Diseases for Oncology version 3 (ICD-O-3) and then into ICD-10. The tumors are then grouped into NORDCAN-specific categories, i.e. NORDCAN entities. Thus far, 41 cancer sites or entities are included in the common database, and the national cancer registries include a separate variable for the NORDCAN entity code.[113] Cancer incidence rates for the general population, grouped according to the NORDCAN entities, can be obtained from their online database.[114]

4.2.1.4 Cause of death registries

The first cause of death registries were established in the mid-20th century (Table 2). Causes of death are derived primarily from death certificates and the registries include the date and place of death, underlying and contributing causes of death, autopsy, and patient demographics. The coverage of the registries is high; for example, the date of death and underlying cause of death in the Swedish registry was 100% and 96% complete, respectively.[115] However, only a few studies have validated the cause of death. One Swedish study compared death certificates to medical records from the final hospitalization, and found 77% agreement between the cause of death on the certificate and the expected cause of death based on the medical records.[116] The agreement was highest for malignant tumors where the death certificates were accurate in 90% of cases.[116] According to a Danish study, 30% of the causes of death were changed after autopsy.[117] Since autopsy rates have dropped significantly since the 1970s and are now completed in only 10% of all deaths in Denmark and Sweden, this might have a negative impact on the quality of death statistics, but its effect seem to vary depending on the cause of death.[115,117]

4.2.1.5 Total population registries

The total population registries in the Nordic countries were established during the 1950s to 70s and are some of the oldest population registries in Europe (Table 2). These registries contain vital statistics such as dates of birth and death, sex, country of birth, citizenship, immigration and emigration, family demographics, and individual and contextual socioeconomic variables.[118,119] The quality of these registries is considered high, especially with regards to data reported by professional or administrative personnel. Self-reported data, such as that of residency and migration, is likely to be of lower quality. It is estimated that close to 100% of all births and deaths in Sweden are reported within 30 days, whereas 5% of immigrations and 9% of emigrations are either reported after 30 days or never reported.[119]

Table 2. National health- and population registries and their year of initiation in five Nordic countries.

Country	Patient Registry	Cancer Registry	Cause of Death Registry	Population Registry
Denmark	1977/1978[a]	1942/1987[b]	1970	1968
Finland	1967	1952/1961[b]	1969	1971
Iceland	1999	1954	1952	1953
Norway	1997	1952/1953[b]	1951	1964
Sweden	1964/1987[a]	1958	1952	1968

[a]Initiation/Nationwide coverage
[b]Initiation/Mandatory reporting

4.2.2 Swedish quality registries

There are more than 100 national quality registries (NQR) in the Swedish health care system with the primary aim to monitor and improve the quality and outcome of care.[120] The NQRs cover a wide range of diseases and areas in the healthcare sector, and have in recent years also become an important source for research. The registries usually include detailed individual-level information on diagnoses, treatments, outcomes, and patient characteristics. Unlike the national health registries, participation in NQR is voluntary both for health care providers and patients. They operate by the opt-out principle, meaning that patients are included in the NQRs unless they actively withdraw after being informed about the registries.[121]

4.2.2.1 Scandinavian Obesity Surgery Registry

The Scandinavian Obesity Surgery Registry (SOReg) was initiated in 2004 and covers all bariatric surgery centers in Sweden since 2013. The inclusion rate of bariatric surgeries performed in Sweden is estimated to 99%.[122] The SOReg contains mandatory information on patient demographics and anthropometric measurements, health care providers, comorbidities, complications, readmissions and reoperations at baseline and 6 weeks, 1 year, 2 years and 5 years post-operative. Optional information includes laboratory test results, blood pressure measurements, use of vitamins and mineral substitutions, and QoL measurements. Additional information on the bariatric surgery is entered after the operation. Completion rates were 100% for the mandatory variables and 67% for the optional ones in 2015.[122]

4.2.3 Medical records

In this thesis, medical records were considered as the "gold standard" against which bariatric surgery registrations in the SOReg and the patient registry were compared. Paper copies of electronic medical records from relevant episodes of care were requested from surgical departments in 44 hospitals around Sweden. The collected medical records included notes from admissions, operations, and discharges.

4.3 Study design

4.3.1 Validation of the bariatric surgery code

In **study I**, bariatric surgery procedures performed in Sweden from January 1 to December 31, 2011 were identified from the SOReg and the Swedish patient registry. A total of 8 501 bariatric surgery registrations were identified from the two registries and divided into five categories (A–E) through cross-tabulation using the personal identity code, hospital name and date of admission (Figure 4):

A. Procedures that are either i) only identified in the SOReg, or ii) identified in both registries but with a non-bariatric surgery code in the patient registry;

B. Procedures that are identified in both registries and matches on admission date and surgical procedure;

C. Procedures that are identified in both registries and matches on admission date, but not surgical procedure;

D. Procedures that are only identified in the patient registry and have a concurrent diagnosis code for obesity;

E. Procedures that are only identified in the patient registry, but without a concurrent diagnosis code for obesity.

4.3.1.1 Sampling strategy

For validation purposes, all registrations from category C, D, E, and non-gastric bypass procedures from category B were selected for validation. Random samples were drawn from procedures in category A and gastric bypass procedures in category B. Sample size was determined based on the assumption of $\geq 95\%$ coherence between medical records and the registries, with a precision of ± 0.03 or less. The sampling procedure was undertaken with assistance from the National Board of Health and Welfare in Sweden.

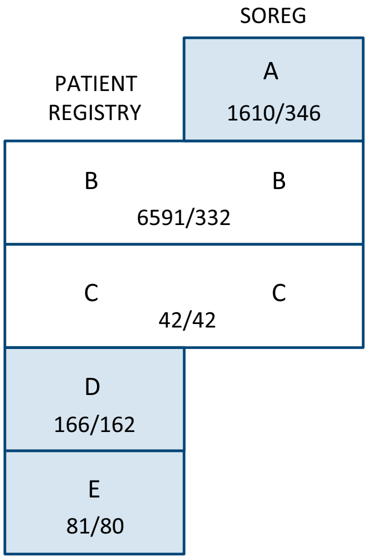


Figure 4. Distribution of bariatric surgery procedures performed in 2011 according to the validation categories (A–E) in the Swedish patient registry and the Scandinavian Obesity Surgery Registry (SOReg). Presented as total number of bariatric surgery procedures/number of validated procedures.

4.3.1.2 Data collection

To enable retrieval of medical records for comparison with the registries, personal identity number, hospital name, and date of admission for the selected episodes of care were provided by the Swedish National Board of Health and Welfare. Information from the medical records was manually extracted based on a predefined template. To evaluate potential auditor bias, double-entry by two reviewers were undertaken for 10% of the medical records and assessed for interrater reliability, which was found to be high (PPV = 92%, kappa value = 0.81).

4.3.2 Nordic Obesity Surgery Cohort

Studies II-IV in this thesis are based on the Nordic Obesity Surgery Cohort (NordOSCo).

The NordOSCo is a population-based retrospective cohort based on registry data from Denmark, Finland, Iceland, Norway and Sweden spanning from 1964 to 2015. There are some differences in study periods between countries due to data availability, i.e. 1976 to 2015 for Denmark, 1968 to 2012 for Finland, 1999 to 2012 for Iceland, 2007 to 2011 for Norway, and 1964 to 2012 for Sweden. While the health and population registries in Norway contain data from several decades back in time, linkages between the registries using a unique personal identifier was not possible prior to 2007.

The cohort includes all individuals who received a diagnosis of obesity in the Nordic patient registries during the study period. For these individuals, all available data from the patient registries were extracted for the study period. To collect additional information, linkages were made to the cancer registries, cause of death registries and total population registries. Figure 5 illustrates the specific variables available in the NordOSCo. When several registries contained the same demographic variable (e.g. sex, date of birth, and date of death), we combined this information from the registries in a step-wise hierarchical fashion to obtain the most complete demographic data.[123]

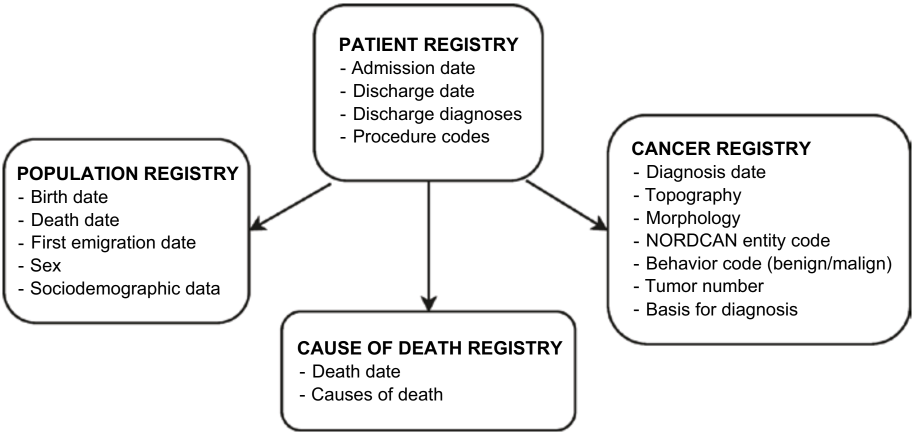


Figure 5. National health and population registries from which data for the Nordic Obesity Surgery Cohort (NordOSCo) were retrieved and the variables included.[123]

4.3.2.1 Inclusion criteria

Figure 6 illustrates the overall data management process and selection of participants into the NordOSCo.

Studies II and III include all individuals in NordOSCo with a diagnosis of obesity aged 18 or above at study entry. Individuals who received a diagnosis of any cancer (**study II**) or any colorectal cancer (**study III**) prior to the date of obesity diagnoses were excluded. **Study IV** includes all Swedish individuals in NordOSCo with an obesity diagnosis and a colon or rectal cancer diagnosis in the Swedish cancer registry. Individuals who received a colorectal cancer diagnosis prior to the

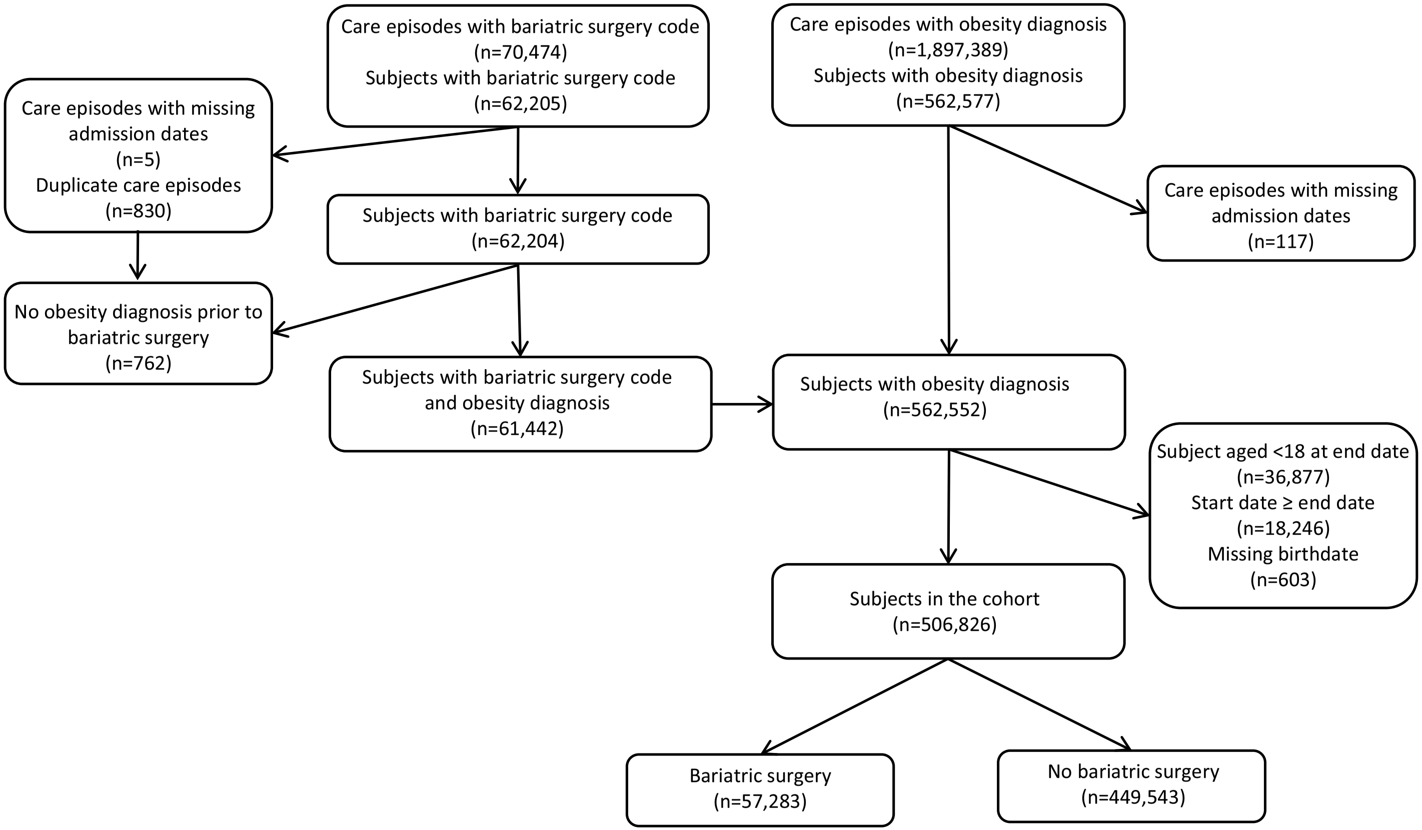


Figure 6. Flowchart illustrating the selection process of participants into the Nordic Obesity Surgery Cohort (NordOSCo).[123]

date of their first obesity diagnosis or date of bariatric surgery were excluded, as well as individuals whose first emigration occurred prior to the colorectal cancer diagnosis.

4.3.2.2 Exposure

The exposure of interest in **studies II-IV** was bariatric surgery. Exposed individuals were identified from operation codes in the patient registries. In Denmark, Finland, Norway, and Iceland, no specific codes for bariatric surgery were available prior to the NOMESCO Classification of Surgical Procedures. Sweden used a country-specific classification system from 1980 to 1996 that contained bariatric surgery codes.

As illustrated in Figure 7, the number of bariatric surgeries performed in the Nordic countries increased rapidly in the 2000s, with highest rates observed for Denmark, Sweden, and Iceland.[123]

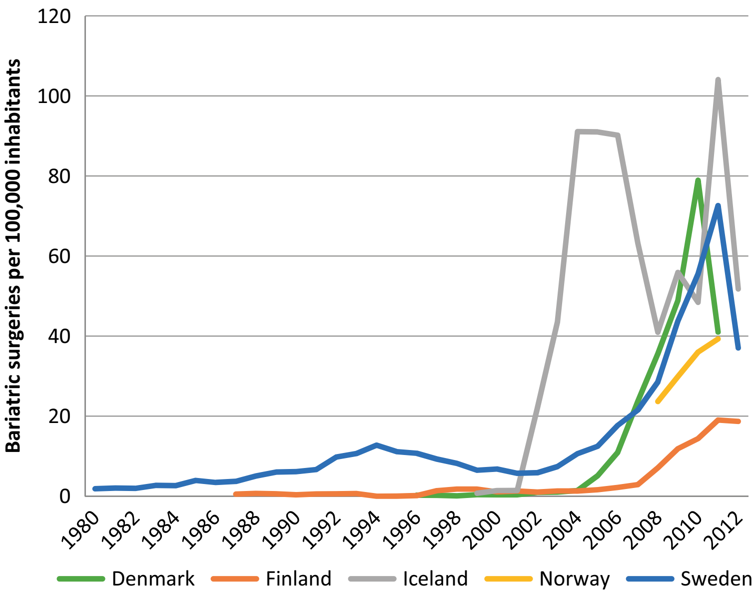


Figure 7. Number of bariatric surgeries per 100,000 inhabitants in five Nordic countries between 1980 and 2012 based on data from the Nordic Obesity Surgery Cohort (NordOSCo).[123]

The predominant type of bariatric procedure has also changed over time. Restrictive procedures such as gastric banding and vertical banded gastroplasty dominated in the 1980s and 1990s, and were mostly performed in Sweden during this time period. Since the 2000s, gastric bypass is the treatment of choice in most cases and outweighs all other bariatric procedures combined (Figure 8).[123] Outside the NordOSCo study period, sleeve gastrectomy has become increasingly popular but the procedure does not have a specific surgical code in NOMESCO. It is, therefore, not possible to separate sleeve gastrectomy from the other bariatric procedures in the patient registry.

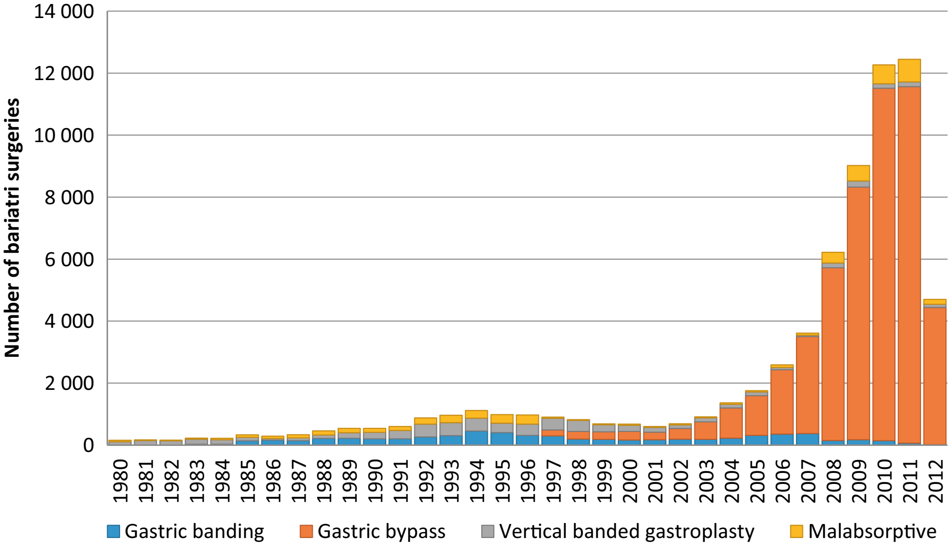


Figure 8. Number of bariatric surgeries by type of procedure performed between 1980 and 2012 in five Nordic countries based on data from the Nordic Obesity Surgery Cohort (NordOSCo).[123]

4.3.2.3 Outcomes

The main outcomes of **study II** were the incidence of any cancer, any obesity-related cancer and any non-obesity related cancer. The definition of obesity-related cancer was based on the viewpoint of the IARC working group and included malignancies from thirteen sites.[4] The cancer events were identified from the national cancer registries and tumor topography was determined based on NORDCAN entity codes. Secondary outcomes included specific tumor sites with a minimum of 20 cancer events in the bariatric surgery group. **Study III** focused on the incidence of colon and rectal cancer that were identified from the national cancer registries using ICD-O-3 codes. The main outcome of **Study IV** was colorectal cancer-specific mortality and the secondary outcome was all-cause mortality. The dates and causes of death were ascertained from the Swedish cause of death registry. Colorectal cancer-specific deaths were identified from ICD codes, and both underlying and contributing causes of death were considered.

4.3.2.4 Study period

Due to limitations in exposure data, as described above, the study periods spanned from 1996-2015 in Denmark, 1997-2012 in Finland, 1999-2012 in Iceland, 2007-2011 in Norway, and 1980-2012 in Sweden. As a result, the population size of **studies II-IV** is smaller than the NordOSCo population, as individuals exited the cohort before the start of study period.

4.4 Statistical analyses

4.4.1 Validation of the bariatric surgery code

To measure the agreement between operative procedures described in the medical records and bariatric procedures recorded in the registries in **study I**, PPV with 95% confidence interval (CI) was estimated.

PPV is most commonly used in the context of diagnostic tests and is defined as the probability that a subject with a positive test truly has the disease. In this case, PPV is the probability that a surgical procedure with a bariatric surgery code in the registry truly is a bariatric surgical procedure according to the medical records ("positive").

$$PPV = \frac{Number\ of\ positive\ bariatric\ surgeries}{Number\ of\ registered\ bariatric\ surgeries}$$

Three PPVs were calculated:

1) Overall concordance, i.e. any bariatric procedure is considered "positive" regardless if the type of procedure is correctly recorded or not;
2) Concordance accounting for the type of bariatric procedure, i.e. the bariatric procedure is considered "positive" only if the specific type of procedure is correctly recorded;
3) Concordance accounting for the type of bariatric procedure and weighted accordingly.

Since non-gastric bypass surgeries were oversampled in the study and misclassification was considered to be more likely for these procedures, a weighted PPV was calculated to adjust for potential underestimation. The assigned weight corresponded to the proportion of the type of procedure among all bariatric procedures in the sample. Thus, more common procedures would have a greater impact on the overall PPV. The statistical analyses were performed using the statistical software SAS 9.4 (SAS Institute).

4.4.2 Nordic Obesity Surgery Cohort

The main statistical methods in **studies II-IV** were survival analysis and indirect standardization. All statistical tests were two-sided and results were considered statistically significant at a 5% significance level. The statistical software STATA 14 (StataCorp LP, College Station, Texas, USA) was used for all statistical analyses.

4.4.2.1 Follow-up

In **studies II and III**, *unexposed* person-time was accumulated from the date of obesity diagnosis (or the inception date of the country-specific study period should it occur after the date of the first obesity diagnosis) until any of the following events, whichever occurred first:

- Diagnosis date for the outcome(s) of interest
- Date of the first bariatric surgery
- Date of death
- Date of first emigration
- End of study period

Exposed person-time was counted from the date of the first bariatric surgery until the outcome(s) of interest, death, emigration, or end of study period. Thus, exposure was treated as a time-varying covariate in the analyses, and an individual who had undergone bariatric surgery could contribute with both unexposed and exposed person-time.

In **study IV**, time to event was defined as time elapsed from the date of the first colon or rectal cancer diagnoses until the date of death, emigration, or end of study period. Exposure status did not change with time in this study, as individuals with a colorectal cancer diagnoses prior to bariatric surgery were excluded.

4.4.2.2 Survival analysis

To evaluate the association between bariatric surgery and the outcomes of interest in **studies II-IV**, the outcome among exposed and unexposed were compared using multivariable Cox proportional hazard models to calculate hazard ratio (HR) with 95% CI. Covariates considered for the final models were based on subject-matter knowledge and formal assessment with the likelihood ratio test and the Akaike information criterion using a backward stepwise approach.

The final model in **study II** included the covariates sex, diabetes, calendar period, length of follow-up, and country. Proxy indicators for tobacco smoking (chronic obstructive pulmonary disease) and excess alcohol consumption (alcohol dependency, and alcohol-induced liver disease, neuropathy, cardiomyopathy, gastritis, and pancreatitis) were also considered but did not significantly improve model fit. In **study III**, the final model adjusted for sex, calendar period, length of follow-up, and country. Based on evidence from literature, T2DM, inflammatory bowel disease, tobacco smoking and excess alcohol consumption were also considered as confounders but were excluded from the final model after formal assessment of model fit. To assess changes in association over time in both studies, separate HRs by follow-up periods were estimated through the introduction of an interaction term between the exposure variable and length of follow-up.

Study IV adjusted for sex, age at colorectal cancer diagnosis, education level, and calendar period. To assess differences in HRs between tumor sites (colon and rectum), an interaction term was introduced between the exposure variable and tumor site. To account for missing data on education level in 4% of the patients, multiple imputation under the missing at random assumption was undertaken.

4.4.2.3 Indirect standardization

To compare cancer incidence rates among individuals in the NordOSCo to cancer incidence rates in the general population, standardized incidence ratios (SIRs) with 95% CIs were calculated separately by exposure group in **studies II and III**. SIR is estimated by dividing the observed number of cancer events to the expected number of events, which is derived from sex-, age- and calendar year-specific cancer incidence rates in the corresponding background population of the Nordic countries. These rates were obtained from the NORDCAN database in **study II** and the national cancer registries in **study III**. Stratified analyses by follow-up periods were also conducted.

4.5 Ethical considerations

Ethical approvals and data retrieval permissions for all studies were sought and granted by the relevant authorities in each country. Registry-based research does not require ethical approval in Denmark and Finland, and is exempt from informed consent in all Nordic countries.

Registry data for **studies II-IV** were delivered stripped of all personal identifiable information. The electronic datasets were stored on university servers or the server of Statistics Denmark, and only accessible to a few individuals involved with data management and analyses for the research project. For **study I**, the Swedish National Board of Health and Welfare conducted the linkage between registries, and personal identity codes were only shared for the individuals whose bariatric surgery procedures were selected for validation. All electronic datasets containing personal identifiable information were password protected and only accessible to a few researchers involved with the study. Paper copies of medical records and datasets on compact discs were stored in safes on locked university premises. For data entry and analyses, personal identity codes were substituted with unidentifiable replacement code. The key between the replacement codes and the personal identity code was erased after completion of the study. Results from all studies in this thesis are presented at the aggregated level.

5 RESULTS

5.1 Validation of the bariatric surgery code

In **study I**, 938 (98%) medical records from 44 clinics were received out of the 962 records requested for validation purposes. Most of the missing medical records belonged to bariatric surgery registrations without a concurrent obesity diagnosis code in the Swedish patient registry (n=19).

The estimated PPVs are presented in Table 3 for the patient registry and the SOReg. There was high agreement between the medical records and the registries, especially for the SOReg. Concordance was higher for gastric bypass than non-gastric bypass procedures. The most common errors included misclassification of sleeve gastrectomy as gastric bypass or vertical banded gastroplasty in the patient registry, and misclassification of rarer types of procedures (such as gastric plication and duodenal switch with prior sleeve gastrectomy) as gastric bypass in both registries. However, misclassification was most common for “non-bariatric” procedures that were incorrectly coded in 17 out of 35 cases in the patient registry, and 2 out of 9 cases in SOReg. “Non-bariatric” procedures included reconstructions to normal anatomy or removal of gastric band after previous bariatric surgery, endoscopic procedures, reoperation due to complications from bariatric surgery, interrupted bariatric surgery, and tumor surgery. Half of the registrations that lacked an obesity diagnosis in the patient registry were bariatric surgeries (n=32), whereas the rest were made up of “non-bariatric” surgical procedures (n=30).

Almost one fifth (n=1,554) of the bariatric surgeries registered in SOReg were not included in the patient registry or were registered with a non-bariatric surgery code in the patient registry (n=56). These missing procedures included mainly gastric bypass (n=1,580), sleeve gastrectomy (n=17), reconstruction to normal anatomy after previous bariatric surgery (n=10), biliopancreatic diversion with duodenal switch (n=2) and other procedures (n=1).

Table 3. Concordance of bariatric surgery registration between medical records and the Swedish patient registry or Scandinavian Obesity Surgery Registry (SOReg), presented as positive predictive values (PPVs) with 95% CI.

Surgical procedure	PPV (95% CI)	
	Swedish Patient Registry	SOReg
Bariatric surgery, overall	97.0 (95.6-98.4)	99.7 (99.3-100.0)
Bariatric surgery, by type of procedure	93.5 (91.5-95.5)	98.6 (97.7-99.5)
Bariatric surgery, by type of procedure and weighted	96.5 (95.0-98.0)	99.7 (99.3-100.0)
Gastric bypass	96.8 (95.1-98.5)	99.8 (99.5-100.0)
Other bariatric surgery	88.6 (83.8-93.4)	97.4 (94.9-99.9)

5.2 Nordic Obesity Surgery Cohort

Table 4. Selected characteristics of individuals in study II-IV from the Nordic Obesity Surgery Cohort (NordOSCo).

	STUDY II	STUDY III	STUDY IV
Total population size	482,572	468,384	1,463
Median follow-up, years			
Exposed	3.1	3.0	3.7
Unexposed	4.2	4.2	4.3
Sex			
Female	326,689	317,217	744
Male	155,883	151,167	719
Median age at study entry, years	45	45	56
Country			
Denmark	195,341	188,340	NA
Finland	83,801	73,741	NA
Iceland	14,850	13,977	NA
Norway	32,408	33,922	NA
Sweden	156,172	158,404	1,463
Bariatric surgery	49,096	48,035	131
Gastric bypass	35,541	36,191	34
Restrictive	10,791	4,108	90
Other	2,764	7,736	7
Main outcome	**Any cancer**	**Colorectal cancer**	**Death**
Exposed	1,314	147	45
Unexposed	24,565	2,912	596

NA=Not applicable

5.2.1 Bariatric surgery and cancer risk

5.2.1.1 Compared to the general population

In **study II**, overall cancer incidence rate among bariatric surgery patients was not increased (SIR 1.00; 95% CI 0.95-1.06) compared to the cancer incidence rate in the corresponding general population. There was a slightly increased risk of non-obesity related cancer (SIR 1.15; 95% CI 1.02-1.29) and a decreased risk of obesity-related cancer (SIR 0.90; 95% CI 0.82-0.99) in this group (Figure 9). In contrast, cancer incidence rates in obese individuals without bariatric surgery were increased by 22% (SIR 1.22; 95% CI 1.19-1.24) compared to the general population, and the risk increase remained significant for both obesity-related and non-obesity related cancers (Figure 9).

The increased risk of non-obesity related cancer among bariatric surgery patients was only statistically significant during the first five years after surgery (SIR 1.36, 95% CI 1.12-1.66). The decreased risk of obesity-related cancer was observed up to a decade post-surgery (SIR 0.80, 95% CI 0.67-0.95 for 0-4 years post-surgery; SIR 0.84, 95% CI 0.72-0.98 for 5-9 years post-surgery).

5.2.1.2 Compared to obese individuals without bariatric surgery

Bariatric surgery patients had a lower overall risk of cancer (HR 0.89; 95% CI 0.83-0.94) compared to obese individuals without this surgery (Figure 10). The lower risk was most evident during the first five years post-surgery (HR 0.77, 95% CI 0.67-0.88 for obesity-related cancers; HR 0.86, 95% CI 0.76-0.99 for non-obesity related cancers).

Sub-analyses by nine tumor sites indicated a decreased risk of breast cancer (HR 0.81; 95% CI 0.69-0.95), endometrial cancer (HR 0.69; 95% CI 0.56-0.84) and non-Hodgkin lymphoma (HR 0.64; 95% CI 0.42-0.97) in women, and an increased risk of kidney cancer (HR 1.44; 95% CI 1.13-1.84) in both sexes after bariatric surgery (Figure 10).

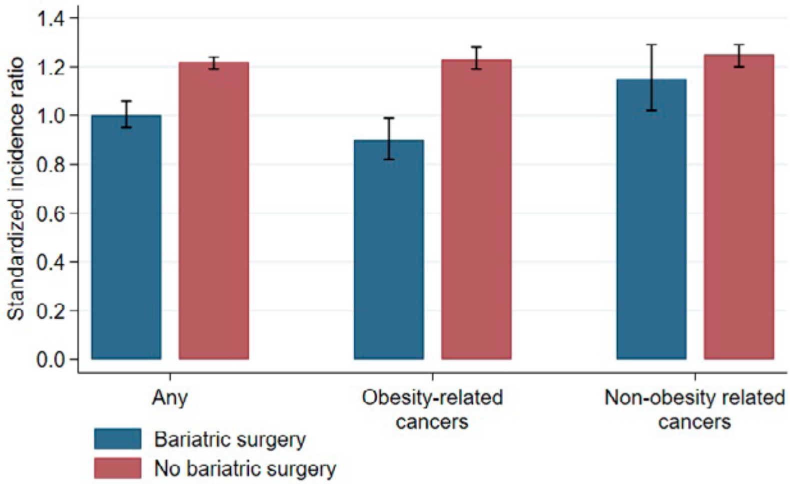


Figure 9. Cancer incidence rates in obese individuals with and without prior bariatric surgery compared to cancer incidence rates in the general population. Presented as standardized incidence ratio with 95% confidence interval.

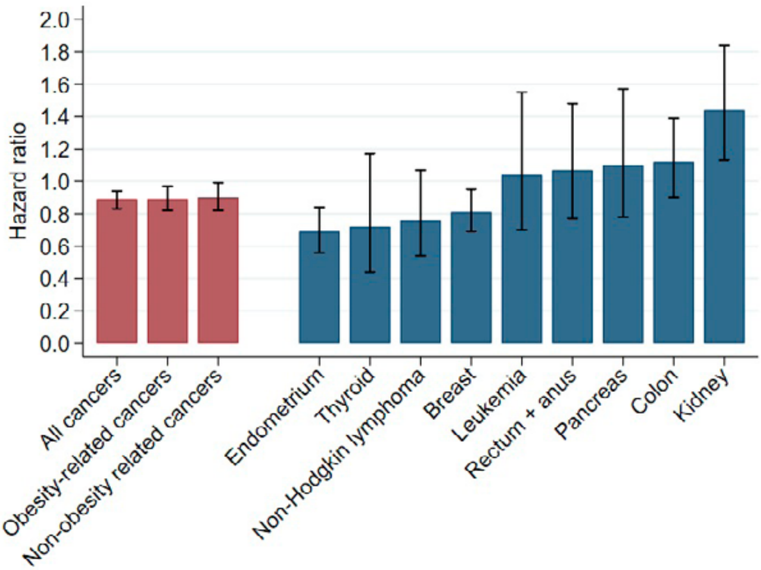


Figure 10. Cancer risk in men and women comparing bariatric surgery patients to obese individuals without bariatric surgery for all cancer, obesity-related cancer, non-obesity related cancer and selected cancer sites. Presented as hazard ratio with 95% confidence interval.

5.2.2 Bariatric surgery and colorectal cancer risk

5.2.2.1 Compared to the general population

In **study III**, the incidence rate of colon cancer among bariatric surgery patients was higher than the corresponding rate in the general population (SIR 1.61; 95% CI 1.32-1.95). This elevated colon cancer risk exceeded that of obese individuals without bariatric surgery (SIR 1.34; 1.28-1.40). There was no increased risk of rectal cancer compared to the general population for either exposure group.

Stratified analyses by follow-up periods indicated that the increased risk of colon cancer among bariatric surgery patients was highest ≥ 10 years after surgery (SIR 2.19, 95% CI 1.41-3.22). In contrast, the risk increase of colon cancer in obese individuals without bariatric surgery remained stable around 30% over time.

5.2.2.2 Compared to obese individuals without bariatric surgery

No statistically significant differences in colon or rectal cancer incidence were observed between bariatric surgery patients and the obese comparison group (Figure 11). Sub-analyses by follow-up periods indicated a possible increased risk of colon cancer with time after surgery, but the difference was only statistically significant for the follow-up period 10-14 years after surgery (HR 1.69, 95% CI 1.11-2.55).

5.2.3 Bariatric surgery and colorectal cancer survival

5.2.3.1 Compared to obese individuals without bariatric surgery

In **study IV**, bariatric surgery patients with a diagnosis of colorectal cancer were compared to obese colorectal cancer patients without previous bariatric surgery. The study identified 32 cases of colorectal cancer-specific deaths and 13 cases of deaths by other causes among patients with colorectal cancer and previous bariatric surgery. The corresponding numbers in the obese comparison group were 354 deaths due to colorectal cancer and 242 deaths due to other causes. A Kaplan-Meier survival plot for bariatric surgery patients and the obese comparison group with colorectal-cancer specific mortality as the outcome is illustrated in Figure 12.

Colorectal cancer-specific mortality (HR 1.50, 95% CI 1.00-2.19) and all-cause mortality (HR 1.62, 95% CI 1.18-2.22) was higher in bariatric surgery patients than the obese comparison group. These findings were primarily driven by a three-fold increase in mortality among rectal cancer patients with bariatric surgery, whereas no significant difference in mortality was observed between the exposure groups with colon cancer (Figure 11).

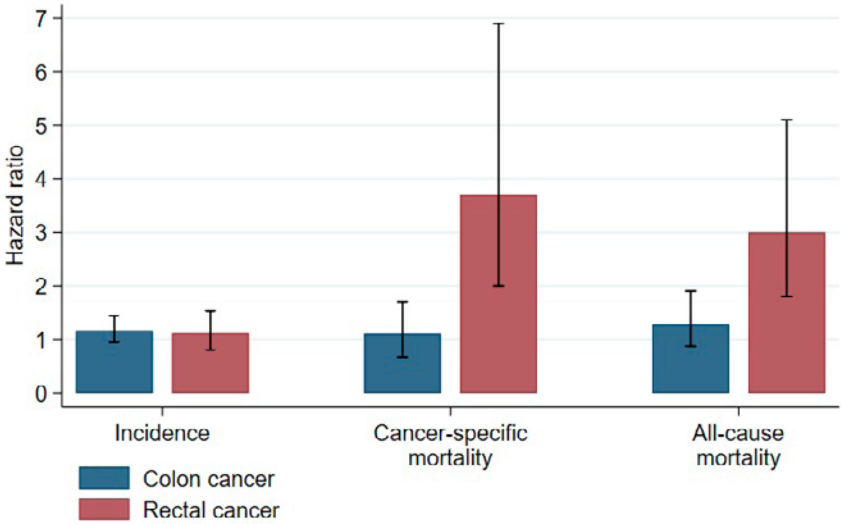


Figure 11. Comparison of cancer incidence, cancer-specific mortality and all-cause mortality between bariatric surgery patients and the obese comparison group, presented as hazard ratio with 95% confidence interval. For mortality estimates, only individuals with a diagnosis of colon cancer or rectal cancer were included.

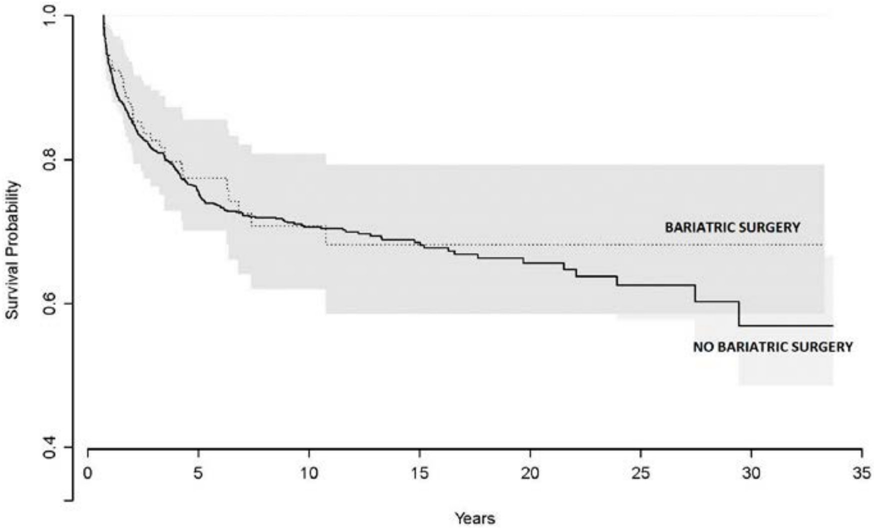


Figure 12. Colorectal cancer-specific survival proportion of obese individuals with and without prior bariatric surgery in Sweden from 1980 to 2012.

6 METHODOLOGICAL CONSIDERATIONS

The robustness of the results in studies I-IV is affected by the study design and the degree to which systematic and random errors appear.

6.1 Study design

Epidemiological studies are observational or experimental. It is generally accepted that well-designed experimental studies generate strongest evidence, as randomization of treatment or exposure increases the likelihood that confounders (observed and unobserved) are equally distributed between exposure groups. It is thus assumed that the only difference between the groups is the exposure. However, random allocation is not always possible or ethically acceptable. In these cases, well-designed observational studies are appropriate.

Studies II-IV in this thesis are observational and retrospective in nature, as exposure and outcomes occurred before cohort enrollment and data collection. The longitudinal cohort design accounts for temporality and ensures that the exposure occurred before the outcome. An alternative to the cohort study could be a quasi-experimental study design where treatment allocation is not random, such as the Swedish Obese Subjects (SOS) study.[3] However, nationwide coverage in five countries would be virtually impossible to achieve with this latter option and require a long period of prospective data collection.

6.2 Validity

Random and systematic errors affect the validity of the study, i.e. the extent to which inferences can be drawn for the source population from which the study sample is obtained (internal validity), and the degree to which results can be generalized to other settings (external validity).[124] Random errors or variations that occur by chance are unpredictable and cannot be replicated by repeating the study. In contrast, systematic errors (or biases) are errors in the design or execution of a study that systematically distorts the association between the exposure and outcome.[124] Figure 13 illustrates the correlation between random and systematic errors.

There are inherent sources of errors affecting the validity of all epidemiological studies. To what extent the study results can be inferred to the source population and the target population depends on the impact of these errors on the direction and magnitude of the results. The validity of the results is therefore based on the judgment of the researchers and the reader.

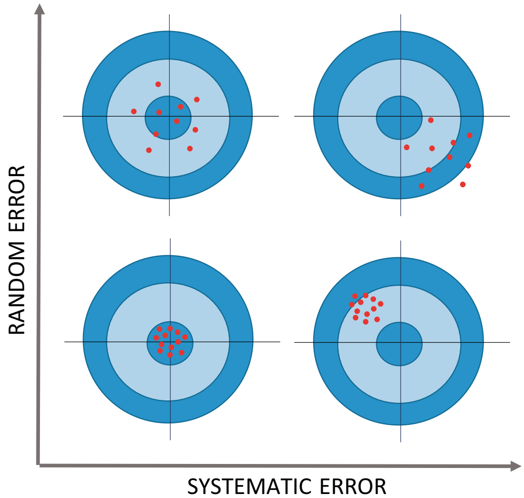


Figure 13. Random error versus systematic error and the effect on validity.

6.2.1 Bias

There are three common types of biases in epidemiological studies: selection bias, information bias, and confounding.

6.2.1.1 Selection bias

Selection bias occurs when the composition of the study sample does not reflect the population for which the results are inferred. Thus, any associations found in the study may not be transferrable to the source population or the target population.

Selection bias in **study I** can be considered low, since either all or a random sample of the bariatric surgery registrations in the different categories were included. Only 2% of the requested medical records were not received, and while the missing records mostly belonged to cases lacking an obesity diagnosis, sensitivity analyses showed limited impact on PPV estimates.

Studies II-IV are nationwide population-based cohort studies that include virtually all patients with a documented obesity diagnosis in any of the five Nordic countries for up to three decades. The risk of selection bias and loss to follow-up can be considered low due to the choice of data sources and study design. Any loss to follow-up most likely to occured in individuals who failed to report their emigration status to the authorities, and is unlikely to differ between exposure groups.

Bariatric surgery in the Nordic countries are predominantly publicly financed and thus captured by the patient registry. Selection bias of exposed individuals should therefore be limited. According to study I, the Swedish patient registry captured > 80% of the bariatric surgery registrations in SOReg in 2011. The missing procedures included mainly gastric bypass and a few sleeve gastrectomy.

The representativeness of obese individuals in the comparison group in relation to the larger Nordic obese population is, however, unknown. No study has validated the obesity diagnoses in the patient registries, and the circumstances under which patients receive an obesity diagnosis during hospitalization is unclear. It is likely that only a fraction of the obese Nordic population is captured through the patient registries, and these individuals may be afflicted with poorer health status. For example, based on self-reported weight and height in the national public health questionnaires, the Swedish Public Health Agency estimated that the prevalence of obesity in the Swedish adult population was 14% in 2012.[125] This is equivalent to 1.15 million adults, a considerably higher number than the Swedish population in NordOSCo. However, low response rates (49% in 2012) and response bias may affect the validity and reliability of the results from the national questionnaires.[126]

In general, identifying a suitable comparison group to study the long-term impact of bariatric surgery is a challenge common to most observational studies due to difficulties in obtaining anthropometric measurements from the general population. A quasi-experimental design could address some of the concerns related to the recruitment of an appropriate comparison group. However, such an approach is likely to seriously limit the study sample size and length of follow-up, and be influenced by biases associated with recruitment of study participants. Another option is to use the medical birth registry that includes information on maternal weight and height upon enrollment in maternity care. However, this would restrict the source population to females who have given birth in the Nordic countries and may limit the study's external validity. Furthermore, a BMI ≤ 30 in the medical birth registry does not necessarily indicate that the individual will not develop obesity at a later point.

6.2.1.2 Information bias

Information bias (or measurement bias) arises from inaccurate measurement or classification of key data such as exposure, outcome, or confounders, and can be categorized as non-differential or differential. The exposure or outcome is equally misclassified between the comparison groups in non-differential misclassification, resulting in risk estimates biased towards the null. In differential misclassification, the misclassification of exposure or outcome is unequally distributed between the comparison groups, and the risk estimates can be biased in either direction.[127]

To address measurement bias of bariatric procedures in **study I**, interrater reliability was assessed and showed high agreement between the investigators, indicating a low risk of systemic misclassification related to the type of bariatric procedure.

Furthermore, study I concluded that the validity of bariatric surgery codes in the patient registry is high, which indicates a low risk of misclassification by exposure in **studies II-IV**.

Misclassification of outcomes in **studies II-IV** can also be considered low. The Nordic cancer registries have overall high completeness and validity. There is some underreporting of cancer cases in the Swedish cancer registry because death certificates are not considered. Since a large proportion of bariatric surgery patients are Swedish, the exposed group may be differentially affected by missed cases. However, the overall proportion of missed cancer events in the Swedish cancer registry is small (4%) and such potential differential misclassification should thus be negligible. Some misclassification may also occur in the categorization of tumor sites due to variations in coding practices between countries, and might affect **study III**. Any such misclassification of tumor sites should be non-differential between exposure groups.

The completeness of the Nordic cause of death registries is also high, and validation studies of these registries indicate that the underlying cause of death is most accurate for malignant tumors.[116] In **study IV**, both underlying and contributing causes of death were considered to ensure that colorectal cancer-specific deaths are captured. This might have overestimated the number of colorectal cancer-specific deaths by misclassifying some cases of deaths due to other causes, but any such misclassification should be non-differential between exposure groups.

Covariates in the models of **studies II-IV** included sex, age at study entry, calendar period, follow-up time, and country. The risk of misclassifying any of these covariates should be low; sex and date of birth were cross-checked between registries, and calendar period and follow-up time were generated automatically from the data. Diabetes was included as a covariate in **study II** and identified from the patient registries. Because most cases of T2DM are treated in primary health care, the patient registries underestimate the prevalence of this disease. This misclassification might be differential since T2DM is an indication for bariatric surgery and therefore less likely to be missed in the exposure group. The impact of this potential bias on the magnitude of the point estimates is, however, difficult to predict. In **study IV**, education level was included as a proxy for socioeconomic status and was derived from the Swedish total population registry that collects this information from different sources, including university and high school registrations, the Swedish public employment service, and the population census.[128] As a result, education level of immigrants might be less accurate, but should be non-differential unless there is an over- or underrepresentation of immigrants in either exposure group.

6.2.1.3 *Confounding*

A confounder refers to a third factor that spuriously affects the association between an exposure and an outcome. It is independently associated with the exposure and outcome without being a part of the causal pathway, in which case it is referred to as a mediator (Figure 14).[127] The confounding effect can be limited or eliminated either in the study design stage or the analysis phase. Adjustment of mediators could partially or completely remove the effect of the exposure on the outcome, and is normally avoided.[127]

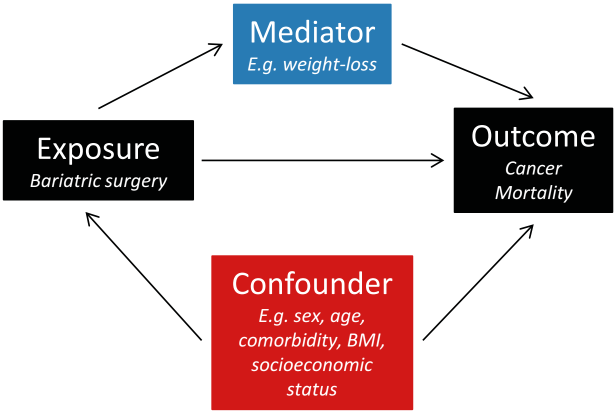


Figure 14. Directed acyclic graph of exposure and outcome in relation to confounders and mediators, exemplified through study II-IV.

Confounding factors were addressed at the analyses stage in **studies II-IV** by adjusting for known factors that might confound the association between the exposure and outcome in multivariable Cox regression models. Selection of covariates to include in the models was based on subject-matter knowledge through literature review and observation of the data. For example, comparison of exposed and unexposed individuals in NordOSCo revealed that the unexposed group is generally older at study entry, more likely to be male, have a higher prevalence of cardiovascular diseases and chronic obstructive pulmonary disease, and a slightly lower prevalence of diabetes and hypertension than the exposed group. Inclusion of covariates in the final model was then determined through model selection based on model fit.

Some potential confounding factors could not be accounted for due to lack of data or insufficient data. These included BMI and behavioral risk factors such as physical activity, nutrition, tobacco smoking, and excess alcohol intake. Proxy indicators were used to assess potential confounding by smoking and excess alcohol use, but were excluded from the final models as they did not improve model fit. However, the lack of effect may have been caused by insufficient data on these two risk factors for cancer. Furthermore, a range of unknown factors may influence the association between exposure and outcome. In the absence of randomization, it is difficult to exclude confounding entirely in epidemiological studies.

6.2.2 Precision

Random error (or random variability) is inversely related to statistical precision. A major contributor to random variation is the selection of study subjects, i.e. sampling. It is assumed that any study population is sampled from a "super-population" that the study applies to. Thus, even population-based studies including entire populations (such as **studies II-IV**) are subject to sampling error. Another source of random error is the unexplained variation in measurements of exposure and outcome, such as the observed cancer incidence or mortality rates in this thesis. Key data on exposures, outcomes, and confounders are therefore subject to both systematic and random measurement errors.[127] One way of improving precision is by increasing sample size, and this approach was taken in **studies II-IV.** By including study subjects from entire populations in the Nordic countries, the study sample was maximized using available data sources. Another possibility is to improve statistical efficiency through study design, for example by matching study subjects on different characteristics.[127]

In statistical analyses, precision is most commonly presented as CI or *P* values. CIs with a level of 95% can be interpreted as the following: if the study was to be repeated numerous times with different samples taken from the super-population at each time and 95% CIs computed for each of them, then 95% of these intervals would contain the true value of the super-population.[127] In simplified terms, CI can be considered as the range of values within which the true value of the super-population is likely to be. In related terms, the *P* value is the probability of observing a difference between comparison groups in the study sample, although no difference exists in the super-population (type I error). If multiple tests are run in a study with a significance level of $P \leq 0.05$, the likelihood of observing statistically significant differences even if no true difference exists is 5%. Strategies to reduce type I errors include lowering the significance level and multiple testing corrections. The consequence of both strategies is an increased risk of type II errors, i.e. failing to observe a statistically significant difference even if a true difference exists. None of these strategies were adopted in **studies I-IV**. Instead, the studies attempted to reduce the number of tests by addressing predefined hypotheses and only considering covariates that were selected based on subject-matter knowledge. Type I error might explain some of the spurious findings in **study II** where an increased risk of kidney cancer among bariatric surgery patients was found, which has rarely been observed in previous studies. Similarly, **study IV** found a strongly increased risk of rectal cancer mortality in bariatric surgery patients that was not seen for colon cancer. Type II errors are counteracted by the large sample sizes in **studies II-III.** However, the power of the test (i.e. the probability of observing a difference in the study sample when there is a true difference) might have been insufficient for sub-analyses by single tumor sites and follow-up periods in **studies II-III**.

6.2.3 Generalizability

External validity or generalizability refers to the extent to which results from the study population can be inferred to populations in other settings.[127] While external validity does not affect internal validity, studies with poor internal validity should not be generalized. The studies in this thesis are population-based and build on nationwide registries of the entire population in one or more Nordic countries. This aspect in itself merits high external validity, unless there is a reason to believe that the mechanisms by which bariatric surgery acts on cancer risk and prognosis differ between the Nordic populations and populations from other settings.

Most of the bariatric surgeries in NordOSCo were gastric bypasses and conducted after the 2000s. Type of bariatric procedure may affect the success rate of long-term weight-loss.[129] Therefore, the study results might be more appropriately applied to this procedure and in modern contexts.

7 GENERAL DISCUSSION

7.1 Validation of the bariatric surgery code

The high level of accuracy in coding of bariatric surgeries in the Swedish patient registry and the SOReg in **study I** confirms that these registries are appropriate data sources for identifying study populations that have undergone bariatric surgery. Given the similarities between the Nordic patient registries, it is reasonable to assume that the level of accuracy for bariatric surgery codes found in the Swedish patient registry is similarly high for the other countries.

Bariatric surgery registrations without a concurrent obesity diagnosis in the patient registry are most prone to errors. Excluding these registrations might increase the specificity of bariatric surgery cases, and this strategy was therefore adopted for **studies II-IV**.

One-fifth of the registered procedures in the SOReg were not found in the patient registry. This indicates, at least in Sweden, that the coverage of bariatric surgeries in the patient registry is incomplete. It is unclear if the same issue is encountered in the other countries. A possible explanation might be lower reporting rates to the patient registry of bariatric surgeries conducted in private practice. Further exploration of the reasons behind these missing cases could be useful to improve the completeness and quality of the patient registry.

7.2 Nordic Obesity Surgery Cohort

Studies II-IV is based on the NordOSCo that is likely to be one of the largest bariatric surgery cohorts to date with some of the longest follow-up. Two previously published retrospective cohort studies on bariatric surgery from England and the United States included larger sample sizes, but the number of bariatric surgery patients was smaller than in the NordOSCo for both studies.[130,131] With up to three decades of follow-up and low risk of loss to follow-up, the NordOSCo is well suited for studying long-term outcomes of bariatric surgery, such as cancer. Although the cohort includes individuals from five countries, the study population can be regarded as rather homogeneous due to similarities in sociodemographic characteristics and genetic profiles, as well as comparable lifestyles, cultures, and health care systems across the Nordic countries.

7.2.1 Bariatric surgery and cancer risk

Results from **study II** indicate that the overall risk of cancer, particularly obesity-related cancer, is decreased after bariatric surgery. The impact was greatest for endometrial cancer, breast cancer, and non-Hodgkin lymphoma in women. The decreased risk of cancer in the endometrium and breast is in line with previously published literature.[80,81] Two studies on bariatric surgery and cancer risk at single tumor sites found no statistically significant association with non-Hodgkin lymphoma, but the point estimates indicated a decreased risk in both cases that were of similar magnitudes as study II.[74,76]

Paradoxically, the risk of kidney cancer was increased after bariatric surgery. The mechanisms behind this finding are unclear; one potential explanation is that bariatric surgery increases the risk of kidney stones that is associated with papillary renal carcinoma.[132,133] In support of this finding, a study from England showed that bariatric surgery patients had a strongly increased risk of kidney cancer compared to the general population, which exceeded the elevated risk of kidney cancer among obese individuals without bariatric surgery.[131]

Although not statistically significant, results from **study II** suggest that the inverse association between bariatric surgery and cancer was strongest during the first five years post-surgery, and that the effect seemed to gradually diminish with time after surgery. The lack of statistically significant associations during the later follow-up periods could be due to smaller sample size. Another potential explanation is that bariatric surgery patients often slowly regain some of the initial weight-loss after surgery, possibly resulting in declining benefits from the surgery.[129] Similar patterns have been observed for other obesity-related comorbidities, such as T2DM and hypertension.[134] The immediate effect of bariatric surgery on cancer incidence is surprising given the typically slow pathogenesis of tumor development and the expected time it may take to reverse the carcinogenic mechanisms. Two possible explanations could contribute to these findings. First, relative contraindications and pre-operative screening for comorbidities might select healthier individuals for bariatric surgery with an overall lower risk of cancer. Alternatively, the comparison group of obese individuals without bariatric surgery identified from the patient registry might have poorer health status and a generally higher risk of cancer than the overall obese population. Second, most bariatric surgery patients with less than five years of follow-up entered the cohort in the latter part of the study period when gastric bypass was the procedure of choice. Gastric bypass typically results in greater weight-loss than restrictive procedures, which might partially explain some of the greater reductions in cancer risk during the early follow-up periods.

7.2.2 Bariatric surgery and colorectal cancer risk

Contrary to the study hypothesis, no statistically significant difference in colorectal cancer rates was observed between bariatric surgery patients and the obese comparison group in **study III**. However, in support of the hypothesis, colon cancer rates in the bariatric surgery population were elevated compared to the corresponding general population, and exceeded that of obese individuals without bariatric surgery. No such trend was observed for rectal cancer.

The impact of bariatric surgery on colorectal cancer risk has been evaluated in a few previous studies with conflicting results. Two North American studies found no impact of bariatric surgery on colorectal cancer risk,[74,76] whereas a meta-analysis of four studies concluded that the risk was reduced.[135] A previous study based on a subset of the Swedish population in NordOSCo found a two-fold increased risk of colorectal cancer in bariatric surgery patients ten years after surgery compared to obese individuals without bariatric surgery.[8] These results were confirmed by a more recent study from England that found an elevated colorectal cancer risk of similar magnitude as the Swedish study, and the risk seemed to increase with time after bariatric surgery.[7] To our knowledge, no prior study has assessed the impact of bariatric surgery on colon and rectal cancer risk separately.

The mechanisms underlying a potential increase in colon cancer risk following bariatric surgery are unclear; hyperproliferation of the bowel mucosa, increased levels of biomarkers, and changes in the gut microbiome resulting from gastrointestinal reconstruction might contribute to the tumorigenesis.[136-138] Furthermore, exposure of the distal bowel to increased levels of bile acids might cause mechanical stress to the mucosal cells that are normally not in contact with these fluids, and could provide some explanation to the observed differences between colon and rectal cancer risk in **study III**. In fact, a study examining the association between cholecystectomy (that results in changes to the bile flow) and intestinal cancer demonstrated a clear gradient effect in which the elevated risk of cancer reduced with increasing distance from the common bile duct.[139] Detection bias might also contribute to the observed higher rate of colon cancer in bariatric surgery patients, as these patients are more likely to be in regular contact with health care during the years following surgery. It does, however, not explain the possible increasing trend of colon cancer incidence with time after surgery.

7.2.3 Bariatric surgery and colorectal cancer survival

Interestingly, **study IV** found a three-fold increase in cancer-specific mortality and overall mortality among rectal cancer patients with previous bariatric surgery compared to obese individuals without this surgery. In contrast, no statistically significant increase in mortality was noted for bariatric surgery patients with colon cancer. These results are unexpected given that individuals who have undergone bariatric surgery seem to be at greater risk of colon cancer than rectal cancer, and there is also a stronger association between obesity and colon cancer than obesity and rectal cancer.[140] Half of the study population lacked information on tumor stage, but among individuals for whom data was available a higher proportion of bariatric surgery patients had stage IV tumors. However, since tumor stage was considered a mediator in the causal pathway between bariatric surgery and cancer survival, we did not adjust for this variable. Other unknown and known potential confounders for which data were lacking (e.g. BMI) might contribute to these spurious findings. Differences in etiology, morphology, tumor behavior, and treatment between colon and rectal cancer might also play a role in the findings, but their potential impact is only speculative at this stage. Finally, we cannot exclude that the observed results for rectal cancer are due to random errors.

7.3 Implications and future research

The beneficial effect of bariatric surgery on morbidity and mortality has been demonstrated in a number of studies. This thesis contributes with additional evidence supporting a protective effect of bariatric surgery on the risk of cancer and provides further arguments in favor of this surgery.

However, a potential increased risk of colon cancer and kidney cancer following bariatric surgery was also identified. Taking available literature into account, these observations might justify heightened awareness of colon cancer in this patient group. Bariatric surgery patients presenting with new onset bowel symptoms should probably undergo colonoscopy promptly to rule out colon cancer, and individuals with additional risk factors for colon cancer might be candidates for screening interventions. The results on kidney cancer are unexpected and warrant further research before any clinical implications can be inferred. If bariatric surgery indeed increases the risk of colon cancer and kidney cancer, identifying patients at higher risk of these cancers could help improve early detection of these tumors. So far, studies on cancer risk after bariatric surgery are mainly observational. The RCTs on bariatric surgery with T2DM as primary outcomes are yet to publish any results on cancer.[59-62] These trials could provide a unique opportunity to study the effect of bariatric surgery on cancer in a controlled setting.

There is a paucity of studies addressing the impact of bariatric surgery on cancer survival after diagnosis. To our knowledge, no previous studies have evaluated the association between bariatric surgery and disease-specific mortality among cancer patients. The unexpected finding of poorer survival in rectal cancer but not colon cancer among bariatric surgery patients in study III warrants further research to confirm a potential association and explore possible underlying mechanisms in order to identify risk groups and interventions. Such studies should also explore the impact of bariatric surgery on cancer survival in other tumor sites.

Overall, identifying individuals who would benefit most from bariatric surgery in the short- and long-term could assist clinicians and policy makers in prioritizing limited health care resources. Large cohorts such as NordOSCo may help in identifying predictive factors for favorable or poor outcomes after bariatric surgery. Future research using NordOSCo would benefit from a better understanding of the comparison group, i.e. individuals with an obesity diagnoses but no bariatric surgery in the patient registry. This can be achieved through a validation study of the obesity diagnosis code through in-depth review of medical records and patient charts that include anthropometric measurements for a randomly selected number of individuals in the cohort. Linkage of NordOSCo to additional health- and population registries would allow access to a range of informative variables. These registries could include the medical birth registry, prescribed drug registry, and quality registries for bariatric surgery in the Nordic countries, amongst others.

With the rising prevalence of obesity globally, demand for bariatric surgery is expected to increase. In 2010, Denmark changed its eligibility criteria for publicly financed bariatric surgery from BMI ≥ 40 kg/m^2 to ≥ 50 kg/m^2.[141] This policy change resulted in a drastic reduction in the number of publicly financed bariatric surgeries.[88] The indication for bariatric surgery in Denmark changed again in 2017 and returned to the original BMI threshold. Policy changes, such as the one adopted in Denmark, offer additional opportunities to study individual- and societal-level impact of bariatric surgery in a natural experiment, and could generate useful evidence to inform policy.

8 CONCLUSIONS

- Registrations of bariatric surgery in the patient registry and the SOReg have a high level of accuracy, and these registries are appropriate data sources for studies on bariatric surgery.
- Bariatric surgery seems to be associated with an overall decreased risk of cancer, with strongest impact on breast cancer, endometrial cancer and non-Hodgkin lymphoma in women. However, the protective effect of bariatric surgery on cancer might decline with time after surgery.
- Bariatric surgery might elevate the risk of colon cancer and kidney cancer, and colon cancer risk might increase further with time after surgery.
- Bariatric surgery might be associated with increased disease-specific and all-cause mortality after rectal cancer diagnosis, but not after colon cancer diagnosis.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund

Fetma är en av vår tids största folkhälsoproblem och ökar risken för flera allvarliga sjukdomar, inklusive diabetes och hjärt- och kärlsjukdomar. Flera studier har också påvisat en tydlig koppling mellan fetma och ökad cancerrisk. FN:s samarbetsorganisation för forskning om cancer (IARC) konkluderade att det finns gott vetenskapligt underlag för att konstatera ett samband mellan fetma och ökad risk för cancer i bröst, livmoder, äggstockar, matstrupe, magsäck, bukspottkörtel, lever, gallblåsa, tjocktarm, ändtarm och benmärg. Det är dock oklart hur viktnedgång påverkar cancerrisken. Det är dessutom okänt hur avsiktlig viktnedgång som inträffat innan cancerdiagnos påverkar överlevnaden i cancersjukdom. Forskning i ämnet försvåras av att konventionella behandlingsmetoder mot fetma sällan leder till uttalad och bestående viktnedgång. Fetmakirurgi är hittills den enda behandlingen med dokumenterade långtidseffekter på viktnedgång och fetmarelaterade sjukdomar. I denna avhandling har ingreppet därför använts för att studera effekten av viktnedgång på cancerrisk och canceröverlevand.

Metoder och resultat

Studierna i avhandlingen bygger på en nordisk kohort (Nordic Obesity Surgery Cohort – NordOSCo) bestående av individer som fått diagnosen fetma registrerad i någon av de nationella patientregistren i Danmark, Finland, Island, Norge eller Sverige mellan åren 1980 och 2012. Kohorten innehåller även information från nationella cancerregister, dödsorsaksregister och befolkningsregister.

I den **första studien** genomfördes en validering av fetmakirurgikoden i det svenska patientregistret och kvalitetsregistret för fetmakirurgi (Scandinavian Obesity Surgery Registry – SOReg). Ett slumpmässigt urval av registrerade fetmaoperation genomförda under 2011 i de båda registren jämfördes mot journaluppgifter. Resultaten påvisade god samstämmighet mellan journaluppgifterna och registren. I patientregistret överensstämde 93.5% av de undersökta fetmaoperationerna, och motsvarande siffra för SOReg var 98.6%. En femtedel av operationerna i SOReg fanns dock inte i patientregistret, vilket talar för inkomplett täckning av fetmaoperationer i detta register. Sammantaget tyder studien på att registren har god tillförlitlighet och kan användas för vetenskapliga studier om fetmakirurgi.

Den **andra studien** undersökte sambandet mellan fetmakirurgi och cancerrisk i NordOSCo. Separata analyser genomfördes för fetma-relaterad cancer, icke fetmarelaterad cancer samt utvalda cancerlokalisationer. Fetmakirurgipatienter jämfördes mot patienter med fetmadiagnos som inte genomgått fetmakirurgi (kontrollgrupp), samt mot bakgrundsbefolkningen. Resultaten visade på lägre cancerinsjuknande efter fetmakirurgi vid jämförelse med kontrollgrupperna, i synnerhet för fetma-relaterad cancer. Störst riskminskning noterades för bröstcancer, livmodercancer och non-Hodgkin lymfom bland kvinnor. Sambanden var starkare tidigt efter fetmakirurgi, och avtog över tid efter operationen. Orsaken till den avtagande effekten är oklar, men kan delvis bero på att vikten hos många patienter successivt ökar igen efter den initiala drastiska viktnedgången. I studien noterades även en ökad risk för njurcancer efter fetmakirurgi, ett samband som behöver utredas i vidare studier.

Den **tredje och fjärde studien** fokuserade på sambandet mellan fetmakirurgi och tjock- samt ändtarmscancer. I den **tredje studien** jämfördes risken för dessa cancrar bland fetmakirurgipatienter i NordOSCo mot samma kontrollgrupper som studie två. Resultaten visade på en 60% ökad risk för tjocktarmscancer bland fetmakirurgipatienter jämfört med bakgrundsbefolkningen. Motsvarande ökning bland patienter med fetmadiagnos och utan fetmakirurgi var 34%. Detta kan tyda på en ökad risk för tjocktarmscancer efter fetmakirurgi, även om det statistiska sambandet inte kunde säkerställas vid den direkta jämförelsen mellan fetmakirurgipatienter och kontrollgruppen med fetmadiagnos. Den ökade förekomsten av tjocktarmscancer var tydligast tio år eller längre efter kirurgi. Inget samband sågs mellan fetmakirurgi och ändtarmscancer.

I den **fjärde studien** undersöktes sambandet mellan fetmakirurgi och överlevnad i tjocktarms- eller ändtarmscancer. I studien jämfördes fetmakirurgipatienter mot kontrollgruppen med fetmadiagnos och inkluderade endast svenska individer som insjuknat i en av dessa cancrar i NordOSCo. Inget samband sågs mellan fetmakirurgi och överlevnad i tjocktarmscancer efter diagnos. Däremot var dödligheten i ändtarmscancer trefaldigt ökad bland cancerpatienter med tidigare fetmakirurgi. Orsaken till den slående skillnaden i överlevnad mellan tjocktarms- och ändtarmscancer bland fetmakirurgipatienter är okänd. Denna studie lyfter för första gången frågan om fetmakirurgins inverkan på canceröverlevnad efter diagnos.

Sammanfattning

Sammanfattningsvis så tyder studierna i denna avhandling på att uppgifter om fetmakirurgi från det svenska patientregistret lämpar sig för forskningsändamål. Den totala cancerrisken verkar minska efter fetmakirurgi. Betydelsen av operationen skiljer sig dock åt mellan olika tumörlokalisationer; störst riskminskning noterades för bröst- och livmodercancer medan en möjlig ökad risk kan föreligga för njur- och tjocktarmscancer. Med hänsyn till det sistnämnda fyndet samt tidigare litteratur är det rimligt att fetmakirurgipatienter som söker med nytillkomna symptom från mag- och tarmkanalen utreds tidigt med koloskopi för att utesluta tjocktarmscancer. Eventuellt kan utökad uppföljning i form av screening beaktas för fetmakirurgipatienter med ytterligare riskfaktorer för tjocktarmscancer. Den ökade dödligheten bland svenska patienter med ändtarmscancer efter fetmakirurgi bör efterföljas av mer forskning för att utreda eventuella samband mellan fetmakirurgi och canceröverlevnad i denna och övriga tumörlokalisationer.

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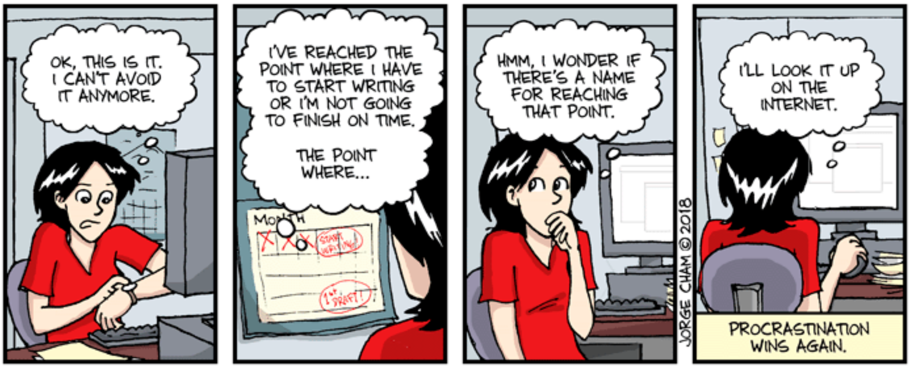

"Piled Higher and Deeper" by Jorge Cham, www.phdcomics.com

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